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# HUMAN PERFORMANCE EFFECTS OF DECREASED CEREBRAL TISSUE OXYGEN SATURATION INDUCED BY VARIOUS LEVELS OF MIXED OXYGEN/NITROGEN

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**FOR THE DIRECTOR**

Thomas J. Moore

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Non-invasive measures of arterial oxygen saturation (Sa02) and regional cerebral oxygen saturation (rS02) were recorded as hypoxic subjects' (N-11) performances were measured on a computer-based cognitive task. One objective was to correlate changes in rS02 (Somanetics INOS 3100 cerebral oximeter) to changes to Sa02 (Nellcor N-200 pulse oximeter). Each subject was instrumented with a cerebral oxysensor, a Nellcor RS-10 oxysensor and EEG electrodes for P300 evoked potential measurement. A Sternberg single-stimulus visual task was to evaluate performance. Hypoxic Sa02 levels of 90%, 80% and 70% were randomized across subjects, and attained using gas mixtures consisting of 12.8%, 11.8% and 10.9% oxygen corresponding to altitudes of 13,000, 15,000 and 17,000 feet. rS02 correlated with the downward trends of Sa02 during desaturation but showed slower return to normal, correlating with failure of subject CNS function to return to normal. There were significant differences in saturation and performance parameters between the 90% target mix and the others, but no consistent difference between the 80% and 70% mixes. CNS deficiencies persisted even though Sa02 had returned to normal.

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# PREFACE

This report documents a series of experiments conducted under Project/Task/Work Unit 72312501 entitled "Aircrew Performance Enhancement." The research was conducted in the Combined Stress Branch (AL/CFBS), Biodynamics and Biocommunications Division, Crew Systems Directorate, Armstrong Laboratory, Wright-Patterson AFB OH.

The authors wish to extend their appreciation to Deepa Naishadham and Charles Goodyear (Logicon Technical Services, Inc.) for their analysis efforts. The research was conducted in-house and supported by the research staff of AL/CFBS. This specific research was completed as partial fulfillment of a Master of Science Degree from Wright State University in Aerospace Medicine by Dr. Arnold. Appreciation is expressed to the AL/CFBS staff, especially SSgt T.C. Cartwright, for their technical support and to the Air Force volunteer subjects who made this research possible.

## TABLE OF CONTENTS


INTRODUCTION.....1

BACKGROUND.....3

Arterial Oximetry.....3

Cerebral Regional Saturation.....10

MATERIALS & METHODS.....15

Subjects.....15

Subject Preparation.....15

Altitude Simulation.....17

Gas Administration.....17

Performance Testing.....18

Test Profile.....20

Data Collection.....21

Data Analysis.....22

RESULTS.....23

General.....23

Saturation Findings.....23

Pulse Findings.....30

Performance Findings.....32

Evoked Potential Findings.....33

DISCUSSION.....38

Oximeter Performance.....38

Heart Rate Response.....40

Performance.....41

Comparison of Gas Mixes.....43

CONCLUSIONS.....45

APPENDICES.....47

REFERENCES.....95

## LIST OF FIGURES

Figure Page


1. Absorption curves of oxyHb and deoxyHb.....9
2. Sensor configuration and mean light paths....12
3. Study Profile.....21
4. Regression Lines for SaO2.....27
5. Regression Lines for rSO2.....27
6. Absolute Differences between Conditions.....29
7. Regression Lines for Pulse.....32
8. Target P300 Amp. and Lat. for 90% Mix.....35
9. Target P300 Amp. and Lat. for 80% Mix.....36
10. Target P300 Amp. and Lat. for 70% Mix.....37

## LIST OF TABLES

Table Page

1. Randomized Test Schedule.....20

2. Sample Population Prebaseline Saturation.....23

3. Time to Desaturation.....24

4. Time to Resaturation.....25

5. Averaged Pulse Rate Data for Conditions.....30

## LIST OF APPENDICES

Appendix Page

A. Consent Form.....47

B. Effect of Sinus Size on Oxisensor.....51

C. Photo: Applying EEG Electrode at Cz.....53

D. Photo: Applying EOG Electrode.....54

E. Photo: Applying Somanetics Oxisensor.....55

F. Photo: EEG Electrode Placement.....56

G. Photo: Leads in Position, with Skull Cap....57

H. Photo: Fully Instrumented Subject.....58

I. Photo: Test Station with INVOS 3100.....59

J. Photo: Laboratory Set-up.....60

K. Prebaseline Saturation Findings.....61

L. Regression Analyses for Subjects.....62

# INTRODUCTION

It has long been recognized that performance is adversely affected by the hypoxia found at altitude[1,2]. In today's high performance jet aircraft, G-tolerance has nearly reached its limit. The combination of both hypoxia and the high-G environment is felt to further deteriorate a pilot's performance, so that additional research is needed to assess the relationship of G-tolerance, the hypoxia of altitude and performance.

In an effort to meet this challenge, a system has been developed that will allow the simultaneous evaluation of performance at high Gz while simulating altitude. This study validates the system in a one Gz environment, prior to installation on the Armstrong Laboratory's Dynamic Environment Simulator/Human Centrifuge (DES).

In addition, it serves to evaluate a new device for the direct, non-invasive, transcranial measurement of cerebral regional oxygen saturation. The recently developed Somanetics Invos 3100 Oximeter uses infrared and near-infrared spectrophotometric methods to give a reading of the hemoglobin oxygen saturation in the region of the cerebral cortex, immediately underlying its sensor.

Given the importance of maintaining adequate oxygen concentration in the brain during many medical

manipulations, from resuscitation to anesthesia to cardiovascular surgery, the utility of such a device is readily apparent. Clinical trials of the device have shown its usefulness in medical settings ranging from carotid endarterectomy[3], to cardiopulmonary bypass,[4] to hypothermic circulatory arrest.[5,6]

This study provides the opportunity to assess the Invos 3100 in a practical controlled environment. It also allows for the assessment of its performance in hypoxic subjects, during recovery from hypoxia, and for the direct comparison with more traditional arterial oximetry.

The current study also allows practical application and assessment of the Psychophysiological Assessment Test System (PATS) in a controlled setting that affects performance.

Another facet of the study serves to assess the expediency of using mixed gas to simulate the hypoxia of altitude.

# BACKGROUND

## Arterial Oximetry

The history of the development of oximetry is a classic example of a technology that did not come about by a single flash of intuition, but rather by the slow, careful incremental work of many separate investigators built on the shoulders of those who went before, even centuries before.

Oximetry's development can be said to have begun when Sir Isaac Newton first discovered the colored spectrum of visible light in the late 17th century. In 1864 Stokes reported his discovery that the colored substance in blood is also the carrier of oxygen. Soon thereafter Hoppe-Seyler crystallized the substance, named it hemoglobin, and demonstrated its color change when mixed with air. In the following decades, Hufner and others defined the dissociation curves of the various hemoglobin species.[7]

In 1880, Herschel demonstrated the existence of a nonvisible radiant energy below the visible red spectrum of light, which became known as infrared. This was followed by the development of infrared optical spectroscopy, which was ultimately used to measure oxygen saturation in human blood by various investigators. Perhaps the best known was the device developed by Millikan (who coined the term

"oximeter"), and used in aerospace investigations into the problem of aviators losing consciousness at high altitude during dogfights in World War II.[8]

Millikan's device warmed the ear lobe, effectively arterializing the tissue, and using light transmitted through the lobe to a sensor on the other side. Little improvement was made on the technology over the subsequent decades, and it remained too inaccurate for clinical application.

Up until 1949, all oximetry was "transmissive", that is, the light had to be beamed through the tissue to a sensor on the opposite side. It was then that Brinkman and Zijlstra demonstrated that the Beer-Lambert law (described below) still applied to reflected red light, and "reflective" oximetry was born.[8] It should be noted that until recently transmissive oximetry was used extensively in neonatal care units, where light was transmitted directly through the frail newborn cranium to an opposing sensor.

Problems persisted though, which stemmed from various difficulties in measuring light in human tissue. These are that the light is scattered by the skin surface, tissue, muscle, bone and blood. Also a certain amount of light is reflected from the skin's surface, which is a function of marked individual variation in skin color and reflectance. Light in the wavelengths used can also be absorbed by non-sanguineous components, affecting the final reflectance. The classic two-wavelength, in-vivo oximetry could not

adequately deal with these variables until the advent of pulse based measurement.[9]

A solution to these difficulties presented itself as a happy accident in 1974, when Aoyagi and his colleagues were attempting to determine cardiac output by measuring dye dilution using noninvasive spectrophotometry. Irritating pulsative variations kept interfering with their readings, so pulse waveform detection was used in an attempt to cancel out the pulsatile noise. They soon realized that the inverse of this technique could provide arterial oxygen saturation by measuring absorbance data at both peak and trough of a detected pulse wave. By canceling out the common elements, they were left with the pulsatile, or arterial, remnant, the absorbance of which represented that of arterial blood.[7] They developed the first pulse oximeter to be clinically utilized and commercially available, the Minolta-Mochida Oximet MET 1471. It was less than successful though, but none-the-less introduced the era of pulse-gaited oximetry.

The early devices depended on bulky fiber optics from incandescent light sources. The development of reliable light-emitting diodes (LEDs) and silicon photo-diode sensors provided lightweight inexpensive means to both transmit and receive light. A convenient coincidence of nature is that the wavelengths in which LEDs are able to transmit happen to be in the red and infrared range.[10]

Other improvements have been made since, primarily in

the introduction of microprocessors, able to perform the complex mathematical algorithms needed, culminating with the introduction of the Nellcor pulse oximeter by the anesthesiologist William New in the early 1980s. This led to the subsequent explosion in the use of oximetry today.

More complete and excellent reviews of the fascinating history behind the development of oximetry have been written by Severinghaus & Astrup (1986), Kelleher (1989), and Tremper & Barker (1989), which have provided immeasurable help in this discussion.[7,8,10]

The basic principles behind oximetry were described early in the Beer-Lambert law, an excellent review of which is given by McCormick et al. (1991), upon which the following is based.[11]

The Beer-Lambert law describes the exponential fall off in intensity of light at a given wavelength (I) as it penetrates living tissue, as the function of three variables: the intensity of the light entering the tissue ($I_\Theta$), the wavelength dependent molar extinction coefficient of the medium (a), and distance light travels through the medium (s). It is given as:

$$I = I_\Theta - e^{as} \qquad (1)$$

This relationship only holds for a nonscattering, homogeneous medium. Tissue though, represents more than a single chromophore. First, human tissue and pigmentation absorb the blue, green and yellow wavelengths, while water

absorbs the longer infrared wavelengths.[9] This leaves the red and near infrared wavelengths. In human tissue, the major chromophores in this range are the hemoglobins. There are other minor chromophores present, but since saturation is a ratio of hemoglobin species, these effectively cancel out. To account for the different chromophores, the equation must be expanded by summing the logarithmic fall off in light intensity due to each chromophore, giving:

$$-\ln I_{(w)}/I_{(w)o} = \sum_{j=1}^{N} a_{(w,j)} C_j s \qquad (2)$$

where $I_{(w)}$ represents the intensity of transmitted light at wavelength w, $I_{(w)o}$ represents the intensity of the incident light at wavelength w, variable a represents the molar extinction coefficient of oxyhemoglobin or deoxyhemoglobin, C represents the content of this molecule in the tissue, and the variable s represents the photon path-length in the tissue.

Unfortunately, this equation cannot be solved quantitatively in-vivo, because the photon path length cannot be known, and the molar extinction coefficients of the chromophores can only be estimated by in-vitro methods. It is possible though, to solve for the clinically relevant ratio of oxyhemoglobin content to total hemoglobin content, i.e. SaO2. By making enough measurements at several wavelengths in the near infrared, a matrix reduction can be used to solve for the oxyhemoglobin/deoxyhemoglobin ratio

(but not the content). This can be illustrated by taking equation 2, and subtracting a second wavelength (w'):

$$-\ln I_{(w)}/I_{(w)o} + \ln I_{(w')}/I_{(w')o} = \sum_{j=1}^{N}(a_{(w,j)}-a_{(w',j)})C_j s \quad (3)$$

The left side of the equation is what is measured at the two wavelengths, and can be represented by the variable M:

$$M_{(w)} = -\ln I_{(w)}/I_{(w)o} + \ln I_{(w')}/I_{(w')o} \quad (4)$$

The difference in extinction coefficients (between the two wavelengths for hemoglobin) is a known, and can be represented with the variable d, as follows:

$$d_w = a_{(w,j)}-a_{(w',j)} \quad (5)$$

It is now possible to simplify equation 3 to:

$$M_w = \sum_{j=1}^{N} d_w C_j s \quad (6)$$

This equation is solved for by making enough (N + 1) measurements to solve for $C_{oxy}$s and $C_{deoxy}$s independently. Again, this does not represent absolute content, but rather is proportional to it. Because the variable s is invariant with wavelengths between 600 and 1000nm,[12] it can be considered constant at the wavelengths utilized, and is canceled out when calculating the oxy-/deoxyhemoglobin ratio. The total hemoglobin content does not change in any physiologically significant way and can also be removed.

This gives:

$$C_{deoxy}{}^{s} / C_{oxy}{}^{s} = C_{deoxy} / C_{oxy} = Hr \qquad (7)$$

Where Hr is the deoxy/oxyhemoglobin ratio, which is converted to SaO2 by:

$$100/(1 + Hr) = 100*[oxyHb]/([deoxyHb] + [oxyHb]) = SaO2 \qquad (8)$$

That two separate wavelengths can be selected to differentiate between oxy- and deoxy hemoglobin is illustrated in Figure 1. It is a fortunate occurrence that these two species, which make up the predominant proportion of hemoglobin in the body, have markedly different absorbances in the infrared-red spectrum. The so-called isobestic point occurs at 803nm, the measurement of which serves as the reference for total hemoglobin (oxyHb + deoxyHb). At this wavelength (in the infrared) the absorbance of oxy- and deoxyhemoglobin are equal. In the

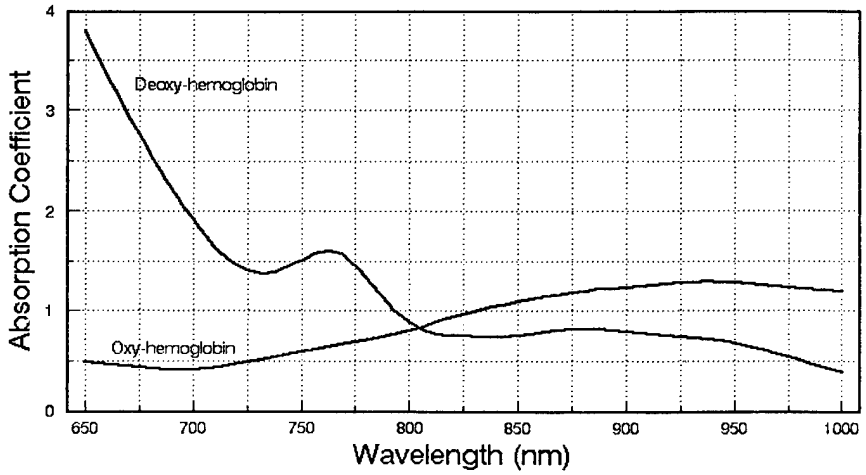


Figure 1. Absorption coefficient of oxy- and deoxyhemoglobin as a function of wavelength in near infrared range. From Klose, et al.[13]

red range, the oxyhemoglobin has markedly less absorbance, leading to increased transmittance of red (lending arterial blood its characteristic color). At 730nm, an absorbance coefficient of .5 corresponds to 100% saturation, whereas an absorbance coefficient of 1.3 corresponds to 0% oxygen saturation.[13] It is these ranges of wavelength that provide the molar extinction coefficients described above.

In practical terms, the probes used in pulse oximetry have two LEDs emitting light in these ranges. The Nellcor N-200 used in this study uses 660nm and 910nm.[7] The Somanetics INVOS 3100 cerebral oximeter, to be discussed in the next section, uses 730nm and 810nm.[14]

The Beer-Lambert law does have difficulties, and is not applicable in a purely theoretical way, as was used by older oximeters, which tended to overestimate the SaO2. Newer oximeters are based on empirical algorithms, which base their calculations on calibration curves derived from studies of a "normal" human population.[7]

More detailed technical explanation of the theory and techniques in arterial pulse oximetry is described by Wukitsch, Pettersen, Tobler and Pologe (1988).[9]

## Cerebral Regional Saturation

In cerebral regional oximetry there is a reversion to the classic, two wavelength, non-pulse oximetry which began in the early 20th century. Jobis (1977) first stated the possibility of using near infrared photospectroscopy in

determining cerebral oxygenation.[15] Its advantages are clear. Whereas pulse oximetry gives an indication of systemic oxygen saturation, it may not reflect the saturation of blood in the brain. With so many medical manipulations aimed at keeping an adequate oxygen supply to the cerebrum, a device that could give a noninvasive, direct measurement of brain oxygenation would be invaluable.

Much of both the history and the technology discussed in the preceding section are applicable to cerebral oximetry, especially the Beer-Lambert law. There are some unique studies though, that laid the groundwork for the final development of the Somanetics INVOS 3100 Cerebral Oximeter.

Eggert & Blazek (1987) undertook cadaveric studies of brain tissue and demonstrated that infrared and near infrared light can penetrate through the skull and scalp into cerebral tissue.[12] Unfortunately, the typical adult head is too thick for direct transmittance through the brain, as has been done with neonates. An alternative to this problem has been described by numerous investigators, primarily Chance and Delpy, who demonstrated "diffuse transmission spectroscopy", where a light path penetrates the cranium and is reflected in all directions, which can be detected by an ipsilateral sensor. With the LED and sensor on the same side, the depth of penetration is a function of the source-sensor distance: i.e., the greater this distance, the deeper the penetration of the mean tissue

photon path into the tissue being sampled.[16]

These principles were used in the development of the Somanetics oxisensor, which is diagramed in Figure 2. It illustrates how a single, multiwavelength LED emits light that essentially follows different arches to the two separate sensors. The near sensor receives light reflected from skin, subcutaneous tissue, and the cranium. The far sensor receives reflectance from those tissues as well as the first few centimeters of the brain. The algorithm then uses the differentiated readings to effectively cancel out (or reduce) the influence of the shallower tissues.

An important distinction from arterial oximetry is that regional cerebral oximetry does not gait off the pulse, and therefore is not an arterial reading. Instead, it is a weighted summation of saturation across all the hemoglobin

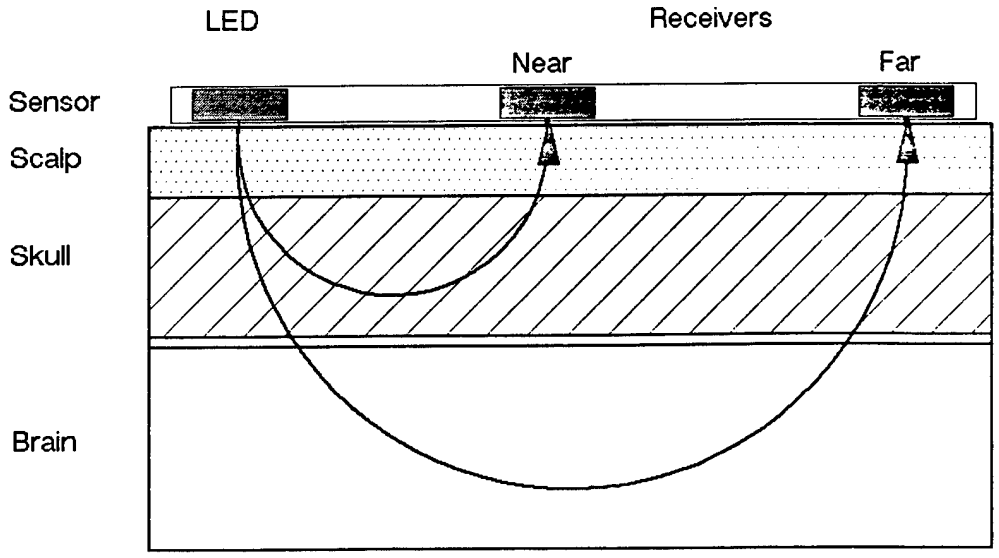


Figure 2. Somanetics oxisensor configuration and mean light paths. Adapted from McCormick et al.[17]

species present in the area of brain immediately under the sensor. (For a discussion of the impact of carboxyhemoglobin and methemoglobin, refer to Wukitsch et al.[9]) It measures the hemoglobin saturation of the entire vascular space, the relative contributions of which are 25% arterial, 70% venous, and 5% capillary.[18] This is referred to as regional hemoglobin, the saturation of which is designated "regional hemoglobin saturation" or rSO2. Since rSO2 represents a mix of arterial and venous blood, the normal range is well below that of SaO2, but greater than venous saturation (SvO2). In a study of 100 randomly selected subjects, Dujovny, Lewis, Vinas, Ausman, Silva & Flemming (1992) found the average rSO2 to be 68.6% +/- 5.6%.[19]

Several studies have been undertaken to validate the INVOS 3100 rSO2 readings. The first of these was done by McCormick, Stewart, Ray, Lewis, Dujovny, & Ausman (1991), who used an anesthetized cat model to directly compare the rSO2 with the actual saturation calculated from SaO2 and mixed venous blood (taken from sagittal sinus). They showed a least-squares positive linear correlation between the two parameters (n=40, r=0.6, s=1.2).[20]

In another study, the same group of McCormick et al. (1992) tested the hypothesis that the INVOS 3100 was reading predominantly cerebral tissue, by selectively injecting the infrared tracer indocyanine green into the internal and external carotid arteries during elective endarterectomies.

When the dye was injected into the internal carotid (ICA), the shallow channel (see Figure 2) did not significantly change. This verifies that the near sensor is indeed reading shallow tissue, since the ICA does not provide circulation to those tissues. In contrast, the deep channel did show major changes indicating the far sensor detected the passage of the indocyanine green through the cerebral vascular system.[16]

Two groups, Koorn, Silvay, Weiss-Bloom, & Neustein (1991), and Prough, Scuderi, Lewis, Stump, & Goetting (1990), have demonstrated that cerebral oximetry rapidly tracked changes in brain saturation produced by ventilatory changes in carbon dioxide (Koorn et al. - hyperventilatory hypocarbia in anesthetized patients, and Prough et al. - $CO_2$ inhalation induced hypercarbia in volunteers).[21,22]

There are case reports available which demonstrate the utility of the INVOS 3100, and cerebral oximetry in general.[23,24]

With the weight of the above evidence, the Somanetics INVOS 3100 Cerebral Oximeter appears to have been developed on sound principles, with adequate validation to justify its use in both the clinical and research arenas.

# MATERIALS AND METHODS

## Subjects

This protocol was reviewed and approved by the Armstrong Laboratory Human Use Review Committee, and by the Wright State University Institutional Review Board. All subjects were voluntary United States Air Force personnel in good physical condition, belonging to the Armstrong Laboratory Sustained Acceleration Stress Panel. Informed consent was obtained from all subjects prior to their participation in this study (see Appendix A). There were eleven (11) subjects used; 8 male and 3 female. The average age was 29.6 years with a range of 25 to 39 years of age.

## Subject Preparation

The subjects were multiply instrumented with electo-encephalographic (EEG) leads to record evoked potentials, a pulse oximeter lead to record SaO2 and pulse, and the Somanetics oxisensor to record cerebral regional oxygen saturation (rSO2).

After craniometric measurement and standard skin cleansing, Biotechnics silver-silver chloride non-invasive EEG leads were placed at the Cz, Pz and Oz scalp positions (apical, parietal, and occipital midline locations

respectively), as well as at retroauricular ground and reference positions. Stable impedance below 5 kilo-ohms was verified for all electrodes.

After skin degreasing and drying, the self-adherent Somanetics oxisensor was placed on the forehead, immediately below the hairline, and fully to the left of the midline (to prevent interference with reflectance due to bony midline structures).[25] All subjects had been transilluminated previously to rule out oversized left frontal sinuses, which could interfere with the Somanetics readings. A more comprehensive discussion of the effect of sinus size on the oxisensor can be found in Appendix B.

A skull cap was placed on the head to protect the EEG sensors during helmet placement. A sized standard HGU-55P Air Force helmet was then carefully applied.

SaO2 and pulse rate were recorded with the Nellcor N-200 Pulse Oximeter. The Nellcor RS-10 oxisensor was placed over the superficial temporal artery immediately anterior to the right ear. It was held in place by pressure from the helmet ear cup. It was placed on the right side, opposite the Somanetics oxisensor, to lessen the possibility of light leakage between the two. The preauricular position of the Nellcor oxisensor has the advantage of being at head level, and has been used previously within the Armstrong Lab's DES.[26] This technique has been validated as comparable to other more standard positions.[27]

Appendices C to H illustrate the instrumentation in

sequence.

## Altitude Simulation

Oxygen/Nitrogen mixtures of 12.8%, 11.8%, and 10.9% oxygen were used to simulate altitudes of 13,000, 15,000 and 17,000 feet above mean sea-level (ft MSL) respectively.[1] The mixtures were commercially prepared and certified. Each of the three gas mixtures were breathed until a target SaO2 was attained, or when the lowest achievable SaO2 for a particular subject was reached. No subject was left on the gas for greater than 30 minutes.

The target SaO2s for mixtures were as follows:

-12.8% (13,000 ft MSL) mix - 90% SaO2

-11.8% (15,000 ft MSL) mix - 80% SaO2

-10.9% (17,000 ft MSL) mix - 70% SaO2

Previous ground-based studies (not using hypobaric chambers) have used gas mixers to "titrate" subjects to the target SaO2, due to individual differences in response to the mixed gases.[28] It was decided to use premixed, tanked gas, given the logistical difficulty in using a mixer within the DES.

## Gas Administration

A fitted MBU-20P Gentex aviator's mask was locked to the helmet and proper seal verified. It was connected to a CRU-93 regulator set to the "normal" setting for room air, and with the experimental gas mixture connected to the "100%

O2" position. Early in the study it was found that there was some experimental gas leaking into the breathing circuit despite the 100% O2 port being turned off, so the experimental gas tank was turned on only during the gas administration period.

## Performance Testing

Subject performance was evaluated by measuring both performance measures (reaction time and error rate), and by event-related evoked brain potentials. The test chosen was an oddball paradigm using a Sternberg single-stimuli, visual, reaction-time test. It has been demonstrated previously as an effective measure of pilot workload, and has had fairly standardized implementation procedures described.[29] Also, it has been shown that a target stimulus set of one, representing about 10 to 20% of the total stimuli, would provoke the greatest evoked potential deflection, the "oddball" paradigm.[30]

The subjects were seated upon a padded generic aircraft seat, with the seat back at 13 degrees from the vertical, approximately 20 inches before a 12 inch computer monitor, on which the visual stimuli were depicted (see Appendix I).

Subject responses were made on a four button response pad that sat upon the lap; one button started the task, one was for all "target" stimuli, and one for all "non-target" stimuli. The fourth button was "dead". Subjects were instructed to use only their index fingers, which were kept in contact with the response keys during testing.

All stimuli were letters of the alphabet; with the letter "X" serving as the target set, and all other non-X letters as the non-target or standard set.

The performance task was administered by the Psychophysiological Assessment Test System (PATS), which is an Apple-based computer system developed at the Armstrong Laboratory. The PATS can be formatted to administer most performance tests and simultaneously record physiological data. The capacity exists of running an entire experiment from stimulus presentation to statistical analysis. It was designed to be a flexible, comprehensive test system for the measurement of psychophysiological data in a wide variety of applications ranging from operational environment with real-world tasks to laboratory environments with standardized tests.[31]

Prior to the fully instrumented blend runs, all subjects were trained on the study task. These practice runs consisted of the same visual one-target memory set to be used in the test runs, but were longer (2 minutes versus one minute). They were administered in sets of ten tests, given on separate days until the reaction times for the set were within approximately 20 milliseconds, and the error rate was no more than one per test for the entire set. If there was any appreciable interval between test runs (approximately 3 to 4 weeks), the subjects were retrained until the above criteria were reestablished.

## Test Profile

When fully instrumented and seated, and with stable saturation and EEG readings, the test run was begun. It consisted of two minutes of prebaseline data followed by the first of three performance tasks. After completion of the one minute task, the subject was switched from room air to the experimental gas, according to a randomized schedule (see Table 1). Desaturation was followed closely, and when the target saturation was reached the second performance test was performed. Following completion of this "gas-task", the subject was placed back on room air, and the resaturation phase begun. When the SaO2 returned to within 2% of the prebaseline normal, the third and final test was given. This was followed by two minutes of post-baseline data. The sequence is graphically represented by Figure 3.

Table 1. Randomized Test Schedule.

| SUBJECT | Blend #1 | Blend #2 | Blend #3 | Data #1 | Data #2 | Data #3 |
|---|---|---|---|---|---|---|
| 1 | 90% | 80% | 70% | 70% | 80% | 90% |
| 2 | 80% | 70% | 90% | 80% | 90% | 70% |
| 3 | 90% | 70% | 80% | 70% | 90% | 80% |
| 4 | 80% | 90% | 70% | 70% | 80% | 90% |
| 5 | 90% | 70% | 80% | 80% | 70% | 90% |
| 6 | 90% | 80% | 70% | 90% | 80% | 70% |
| 7 | 70% | 80% | 90% | 70% | 90% | 80% |
| 8 | 70% | 80% | 90% | 80% | 90% | 70% |
| 9 | 70% | 90% | 80% | 90% | 70% | 80% |
| 10 | 80% | 90% | 70% | 90% | 80% | 70% |
| 11 | 70% | 90% | 80% | 80% | 70% | 90% |

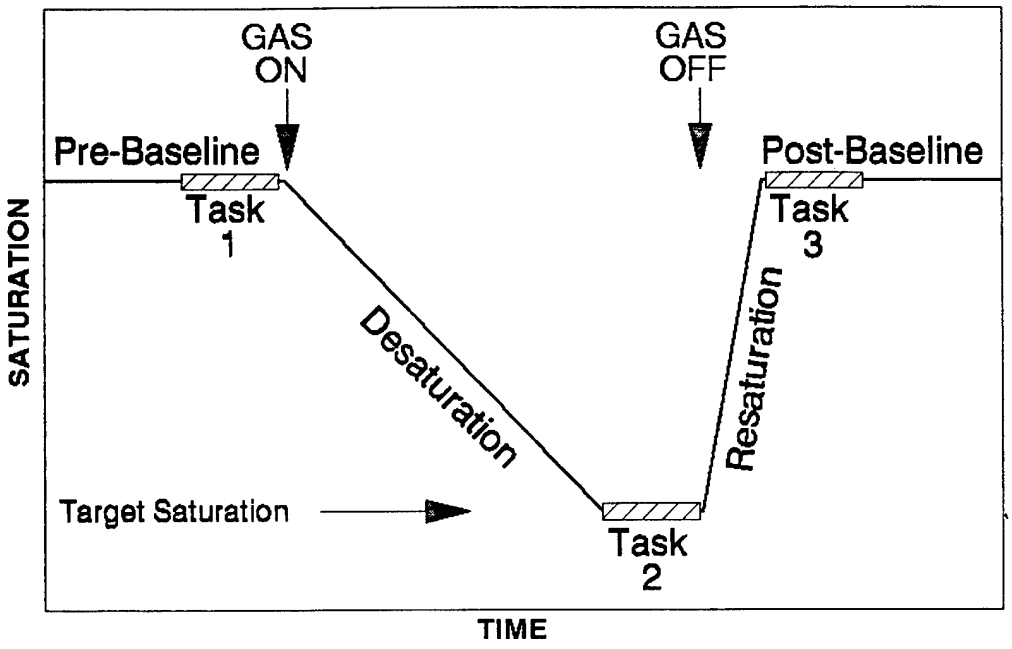


Figure 3. Study Profile.

A feature of the study was that each set of experimental gases was administered twice. The first set was to accustom the subject to the "blended" components of the study. In the "blend" runs, the gas-induced hypoxia, performance task and full instrumentation were experienced together for the first time. This was essentially practice for the second set, or "data" runs, in order to reduce any novelty or anxiety induced bias. The blend and data runs could be combined if no significant difference exists between them.

## Data Collection

The PATS was used to collect all performance data at 1000 Hertz for later analysis. It also collected saturation data (SaO2 & rSO2) during the testing periods only. A

Zenith 248 PC-compatible computer with an analog-digital board was used to collect and store SaO2, rSO2, heart rate and time code data at a rate of one Hertz. Event marking capability was used to mark time of the different periods of the data run.

The arrangement of the systems and test station is shown in Appendix J.

## Data Analysis

For each subject, the EEG data collected by the PATS was analyzed to determine the average P300 amplitude and latency for each task performed.

Further data analysis was done on microcomputers using commercially available spreadsheet and statistical programs.

Data weres evaluated by multivariate and univariate ANOVA, with any globally significant findings subjected to pairwise t-test comparisons and Newmaul/Keul's Procedure.

# RESULTS

## General

The study runs were tolerated well by all subjects, and there were no terminations due to subject symptomatology or complaint. In general, all symptoms experienced were reported to be the same as or similar to that which the subjects had encountered within altitude chamber exposures. These included some sweating, malaise, feelings of claustrophobia and mild headaches.

## Saturation Findings

The average prebaseline SaO2 and rSO2 values for all 11 subjects were 99.38% and 64.39% respectively, with corresponding standard deviations and ranges represented in Table 2. Individual subject data broken down into blend and data runs as well as all runs are given in Appendix K.

Table 2. Sample Population Prebaseline Saturation.

| | SaO2 | rSO2 |
|---|---|---|
| Aver. | 99.38 | 64.39 |
| S.D. | 0.95 | 3.62 |
| Range | | |
| Min. | 98.24 | 55.10 |
| Max. | 100.00 | 70.67 |

As can be seen in Table 3, the desaturation time (time from initial gas change to beginning of second task) varied moderately between individuals, and less so between individual runs of each subject. There was no significant

Table 3. Time to Desaturation (minutes).

| SUBJ | BLEND | | | DATA | | | AVER | | |
|---|---|---|---|---|---|---|---|---|---|
| | 70 | 80 | 90 | 70 | 80 | 90 | 70 | 80 | 90 |
| 1 | 25.95 | 18.35 | 3.65 | 15.27 | 17.60 | 4.80 | 20.61 | 17.98 | 4.23 |
| 2 | 8.93 | 6.72 | 3.70 | 11.25 | 11.18 | 3.93 | 10.09 | 8.95 | 3.82 |
| 3 | 10.12 | 5.92 | 2.72 | 7.15 | 4.75 | 2.68 | 8.63 | 5.33 | 2.70 |
| 4 | 17.87 | 7.72 | 4.20 | 11.10 | 8.28 | 6.52 | 14.48 | 8.00 | 5.36 |
| 5 | 5.78 | 8.67 | 2.87 | 5.38 | 4.72 | 3.43 | 5.58 | 6.69 | 3.15 |
| 6 | 25.87 | 16.77 | 4.85 | 19.15 | 12.23 | 7.20 | 22.51 | 14.50 | 6.03 |
| 7 | 24.67 | 8.58 | 6.65 | 26.75 | 17.53 | 7.42 | 25.71 | 13.06 | 7.03 |
| 8 | 15.37 | 13.65 | 13.65 | 12.28 | 23.35 | 21.12 | 13.83 | 18.50 | 17.38 |
| 9 | 8.57 | 9.28 | 8.37 | 10.85 | 8.17 | 3.72 | 9.71 | 8.73 | 6.04 |
| 10 | 10.05 | 26.55 | 13.85 | 18.52 | 21.15 | 13.58 | 14.28 | 23.85 | 13.72 |
| 11 | 13.40 | 14.20 | 9.88 | 20.88 | 17.63 | 6.17 | 17.14 | 15.92 | 8.03 |
| GRP_AV | 15.14 | 12.40 | 6.76 | 14.42 | 13.33 | 7.32 | 14.78 | 12.86 | 7.04 |
| GRP_ST | 7.09 | 6.28 | 4.13 | 6.38 | 6.49 | 5.47 | 6.25 | 5.84 | 4.58 |
| RANGES | | | | | | | | | |
| MIN | 5.78 | 5.92 | 2.72 | 5.38 | 4.72 | 2.68 | 5.58 | 5.33 | 2.70 |
| MAX | 25.95 | 26.55 | 13.85 | 26.75 | 23.35 | 21.12 | 25.71 | 23.85 | 17.38 |
| | 70B-80B | 80B-90B | 70B-90B | 70D-80D | 80D-90D | 70D-90D | 70A-80A | 80A-90A | 70A-90A |
| t= | 1.07 | 3.68 | 3.11 | 0.68 | 4.83 | 3.20 | 1.55 | 4.97 | 3.61 |
| p= | 0.1555 | 0.0021 | 0.0055 | 0.2574 | 0.0003 | 0.0048 | 0.1581 | 0.0003 | 0.0024 |

difference between the blend and data run times, so they were combined. The overall average desaturation time to the 70%, 80% and 90% target SaO2s were 14.78, 12.86 and 7.04 minutes respectively. The range of times may be found in Table 3. ANOVA demonstrated a significant F-ratio for the combined data ($F(2,30)=5.69$, $p=.008$). Paired t-tests were

significant between the 70% and 90% times (t=3.61, p=.0024), and between the 80% and 90% times (t=4.97, p=.0003). There were no significant differences for the time to target desaturation between the 70% and 80% tests. This pattern was verified by the Newmaul/Keul's Procedure to the .05 confidence level.

In Table 4, the resaturation time for all subjects along with the averages is shown. The overall time to

Table 4. Time to Resaturation (minutes).

| SUBJ | BLEND | | | DATA | | | AVER | | |
|---|---|---|---|---|---|---|---|---|---|
| | 70 | 80 | 90 | 70 | 80 | 90 | 70 | 80 | 90 |
| 1 | 2.07 | 1.08 | 1.03 | 3.32 | 1.73 | 1.17 | 2.69 | 1.41 | 1.10 |
| 2 | 1.70 | 2.13 | 0.40 | 0.73 | 1.28 | 0.77 | 1.22 | 1.71 | 0.58 |
| 3 | 0.82 | 1.77 | 0.52 | 1.15 | 2.50 | 1.02 | 0.98 | 2.13 | 0.77 |
| 4 | 0.70 | 2.18 | 0.73 | 0.95 | 0.47 | 0.60 | 0.83 | 1.33 | 0.67 |
| 5 | 2.40 | 2.03 | 2.13 | 2.42 | 2.48 | 1.15 | 2.41 | 2.26 | 1.64 |
| 6 | 0.65 | 0.72 | 1.60 | 0.98 | 0.52 | 1.10 | 0.82 | 0.62 | 1.35 |
| 7 | 3.38 | 1.23 | 0.57 | 0.53 | 0.83 | 1.00 | 1.96 | 1.03 | 0.78 |
| 8 | 2.00 | 0.55 | 0.77 | 1.30 | 1.00 | 0.63 | 1.65 | 0.78 | 0.70 |
| 9 | 3.20 | 1.30 | 1.60 | 2.77 | 2.58 | 1.82 | 2.98 | 1.94 | 1.71 |
| 10 | 1.82 | 2.28 | 1.07 | 1.20 | 0.87 | 1.67 | 1.51 | 1.58 | 1.37 |
| 11 | 0.75 | 0.72 | 0.85 | 1.07 | 2.22 | 1.43 | 0.91 | 1.47 | 1.14 |
| GRP_AV | 1.77 | 1.45 | 1.02 | 1.49 | 1.50 | 1.12 | 1.63 | 1.48 | 1.07 |
| GRP_ST | 0.93 | 0.65 | 0.54 | 0.91 | 0.83 | 0.39 | 0.78 | 0.53 | 0.40 |
| RANGES | | | | | | | | | |
| MIN | 0.65 | 0.55 | 0.40 | 0.53 | 0.47 | 0.60 | 0.82 | 0.62 | 0.58 |
| MAX | 3.38 | 2.28 | 2.13 | 3.32 | 2.58 | 1.82 | 2.98 | 2.26 | 1.71 |
| | 70B-80B | 80B-90B | 70B-90B | 70D-80D | 80D-90D | 70D-90D | 70A-80A | 80A-90A | 70A-90A |
| t= | 0.90 | 1.65 | 2.45 | -0.02 | 1.70 | 1.48 | 0.65 | 2.43 | 2.79 |
| p= | 0.1953 | 0.0654 | 0.0171 | 0.5086 | 0.0602 | 0.0845 | 0.2660 | 0.0177 | 0.0096 |

resaturate from the 70%, 80% and 90% target SaO2 levels were 1.63, 1.48 and 1.07 minutes respectively, with the corresponding ranges as shown. Analysis of variance showed

no significant differences in the times to resaturation among the mixes. However, trends were similar to the desaturation values above; that is, time to resaturation showed 70% > 80% > 90%.

In order to study the correlation between the desaturation slopes of the SaO2 and the rSO2, lines of regression were drawn through each set of data, with the results shown in Appendix L. It is readily evident from examination of the graphs in the Appendix that quite tight data were utilized for each individual regression line. These data were averaged across all subjects, and are graphically represented in Figures 4 and 5. These show the average regression lines for desaturation, resaturation, and both baselines for the SaO2 and rSO2 respectively.

In Figure 4, which represents SaO2, the prebaseline values were level within the normal clinical range. During the desaturation, the lower the O2 concentration of the mixed gas, the steeper was the slope of desaturation, and the more profound the hypoxia. As demonstrated earlier, the resaturation was very quick, with rapid convergence of the slopes for all gases. The point of that convergence was very near the prebaseline levels. All slopes were significantly different between each gas mix during both desaturation ($F(2,20)=53.53$, $p=.0001$), and resaturation ($F(2,20)=17.74$, $p=.0001$). There was no significant difference between the pre- and postbaseline levels or slopes.

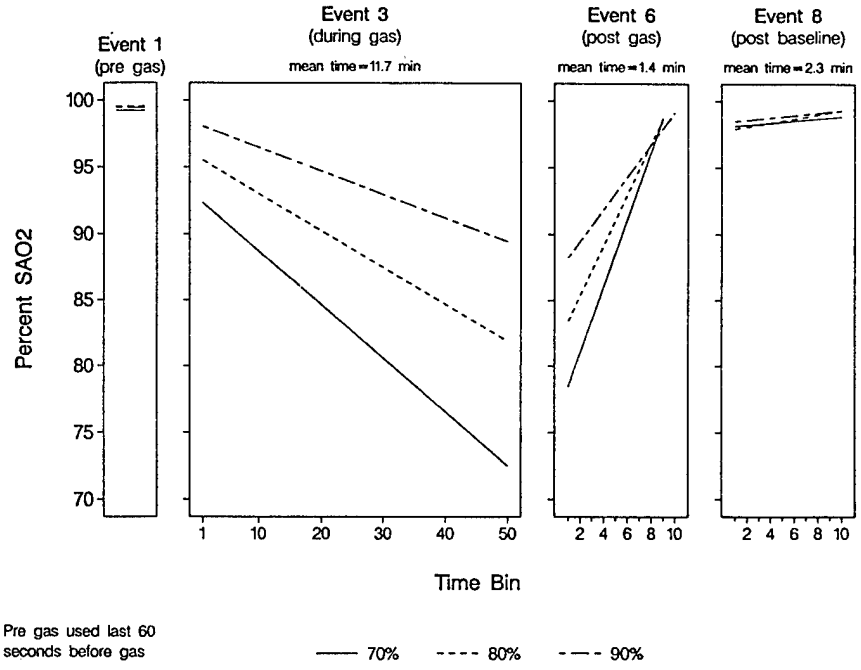


Figure 4. Averaged Regression Lines for Prebaseline (Event 1), Desaturation (Event 3), Resaturation (Event 6), and Postbaseline (Event 8) for SaO2.

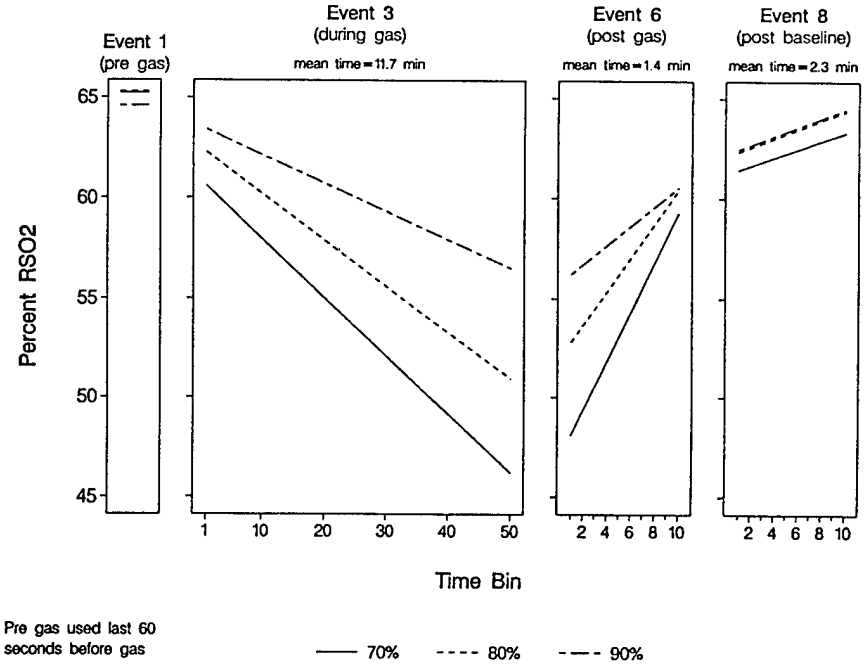


Figure 5. Averaged Regression Lines for Prebaseline (Event 1), Desaturation (Event 3), Resaturation (Event 6), and Postbaseline (Event 8) for rSO2.

Figure 5 shows slopes for the rSO2. The same pattern of steeper slope and more profound hypoxia with incremental lessening of oxygen content of the mixes is seen as with the SaO2 slopes. The slopes for rSO2 during both desaturation and resaturation were significantly different across the gas mixes (desaturation: $F(2,20)=21.26$, $p=.0001$; resaturation: $F(2,20)=22.92$, $p=.0001$). No difference existed between the slopes of the gas mixes during the postbaseline period. In contrast to the SaO2 pattern, the rSO2 resaturation lines fail to approach the prebaseline levels and only slightly converge. The postbaseline slopes showed continued resaturation throughout the period, being significantly different from the prebaseline ($F(1,18)=7.14$, $p=.0254$).

Another aspect of the saturation data is shown in Figure 6. Under the SaO2 title, is illustrated the absolute difference between the prebaseline SaO2 values and the average maximum desaturation SaO2 for each gas mix, next to the absolute difference between the prebaseline and postbaseline SaO2 values. The average actual SaO2s at desaturation were 75.1%, 83.5% and 90.7%, for the target levels of 70%, 80% and 90% respectively. The changes between the prebaseline and desaturation SaO2 conditions were all highly significant ($F(2,20)=102.86$, $p=.0001$). The difference between the pre- and postbaseline SaO2s was negligible and nonsignificant, which was expected given that normal SaO2 indicated the end of resaturation.

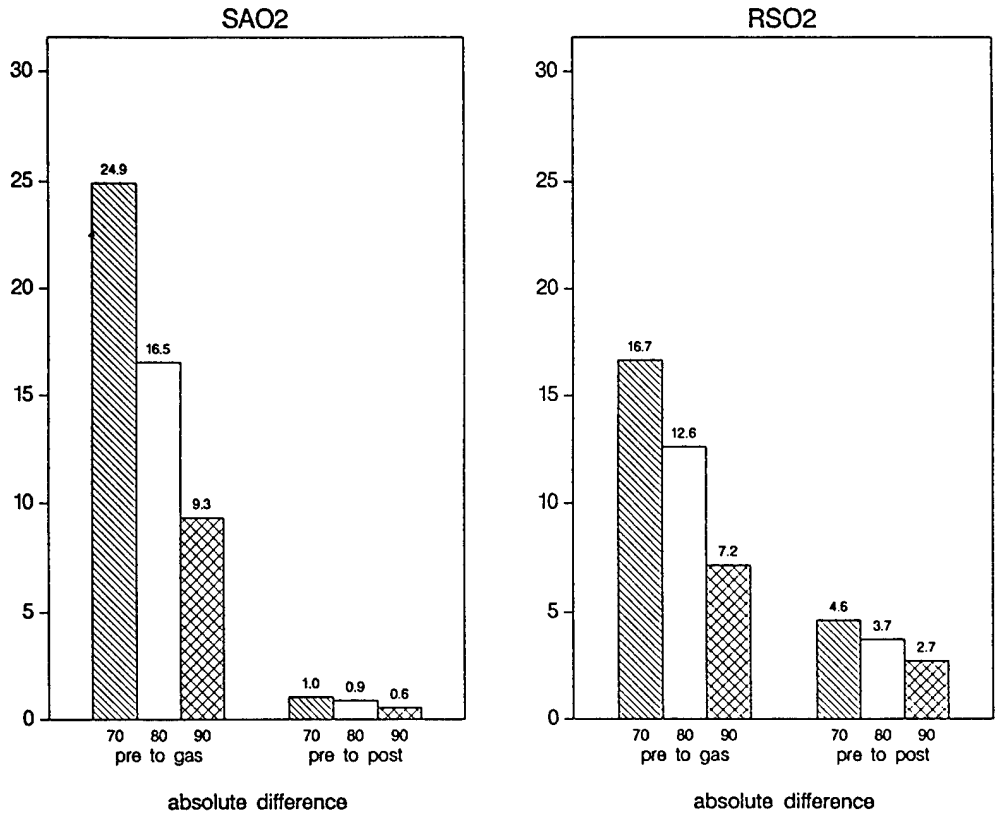


Figure 6. Absolute Differences between Prebaseline and Desaturated (Gas) Conditions, and between Prebaseline and Postbaseline Conditions for each Experimental Gas: SaO2 compared with rSO2.

Also in Fig. 6, the rSO2 data show a smaller absolute difference, but this is only a matter of scale, since normal rSO2 levels range from 55 to 70% versus 98 to 100% for SaO2. The average decrease in rSO2 was 16.7% while breathing the 70% target gas, 12.6% for the 80% target mix, and 7.2% for the 90% target mix, and were significantly different ($F(2,20)=31.68$, $p=.0001$). In contrast to the SaO2 data, a significant difference exists between the prebaseline and postbaseline rSO2 values ($F(2,20)=3.50$, $p=.0498$).

## Pulse Findings

The pulse rate generally followed the expected pattern of increase during hypoxia, and return towards normal following resaturation. The trend was for an increase in pulse rate during the desaturation, with all subjects showing a decrease in pulse during the resaturation. The mean postbaseline rate was lower than prebaseline, but this was not significant. There was a continued drop in the pulse during the postbaseline period. The pulse rate data is summarized in Table 5.

Table 5. Averaged Pulse Rate at Prebaseline, Desaturated, and Postbaseline Conditions.

(Averaged Blend and Data Runs)

| | AVERAGED 70% RUNS | | | AVERAGED 80% RUNS | | | AVERAGED 90% RUNS | | |
|---|---|---|---|---|---|---|---|---|---|
| Subj | PRE- | DESAT- | POST- | PRE- | DESAT- | POST- | PRE- | DESAT- | POST- |
| 1 | 64.20 | 76.76 | 61.58 | 62.22 | 75.22 | 60.49 | 61.05 | 72.82 | 61.73 |
| 2 | 82.72 | 97.91 | 79.94 | 84.13 | 90.56 | 79.79 | 77.09 | 83.77 | 78.90 |
| 3 | 87.77 | 101.81 | 83.70 | 82.46 | 98.25 | 81.57 | 85.79 | 94.13 | 85.28 |
| 4 | 63.41 | 89.19 | 66.15 | 63.84 | 73.61 | 66.15 | 67.87 | 80.48 | 66.92 |
| 5 | 68.15 | 74.93 | 61.90 | 75.91 | 84.55 | 68.30 | 68.31 | 81.51 | 66.93 |
| 6 | 56.45 | 67.60 | 57.58 | 62.40 | 66.99 | 61.85 | 58.28 | 64.31 | 61.52 |
| 7 | 68.66 | 75.33 | 64.71 | 71.33 | 73.23 | 67.94 | 65.28 | 69.29 | 60.45 |
| 8 | 78.13 | 82.36 | 72.33 | 70.75 | 73.47 | 66.27 | 69.33 | 74.18 | 69.69 |
| 9 | 67.74 | 85.69 | 62.73 | 65.44 | 79.50 | 63.90 | 70.04 | 79.77 | 66.08 |
| 10 | 82.05 | 87.91 | 70.25 | 73.53 | 82.35 | 68.52 | 79.22 | 81.41 | 70.96 |
| 11 | 62.69 | 72.71 | 63.86 | 57.77 | 70.49 | 64.95 | 64.87 | 70.18 | 67.21 |
| AVER. | 71.09 | 82.93 | 67.70 | 69.98 | 78.93 | 68.16 | 69.74 | 77.44 | 68.70 |

When average pulse rate for the prebaseline,

desaturated and postbaseline conditions were analyzed globally within each gas mix, they were found to be significantly different (70%- $F(2,30)=7.5$, $p=.0023$; 80%- $F(2,27)=5.22$, $p=.0121$; 90%- $F(2,27)=3.74$, $p=.0369$), with Newman/Keul's Range Test showing significance between the desaturated condition and both pre- and postbaseline conditions at the .05 confidence level. There was no significant difference between the pre- and postbaseline conditions. This pattern was the same for all three gas mixes. In contrast, there was no statistically significant difference when sought between the gas mixes at each task condition (prebaseline, desaturated and postbaseline). That is, the pulse rate reacted the same despite the gas mixture.

Regression analysis of the slopes of heart rate response during the desaturation, resaturation and postbaseline conditions are shown in Figure 7. The only significant difference between the gas mixes was during resaturation ($F(2,20)=6.66$, $p=.0061$). Pairwise t-test analysis shows significance between the 90% and 70% mixes ($t=3.62$, $p=.0047$), and between the 90% and 80% mixes ($t=2.38$, $p=.0388$). There was no significant difference between the slopes of the 80% and 70% mixes during resaturation.

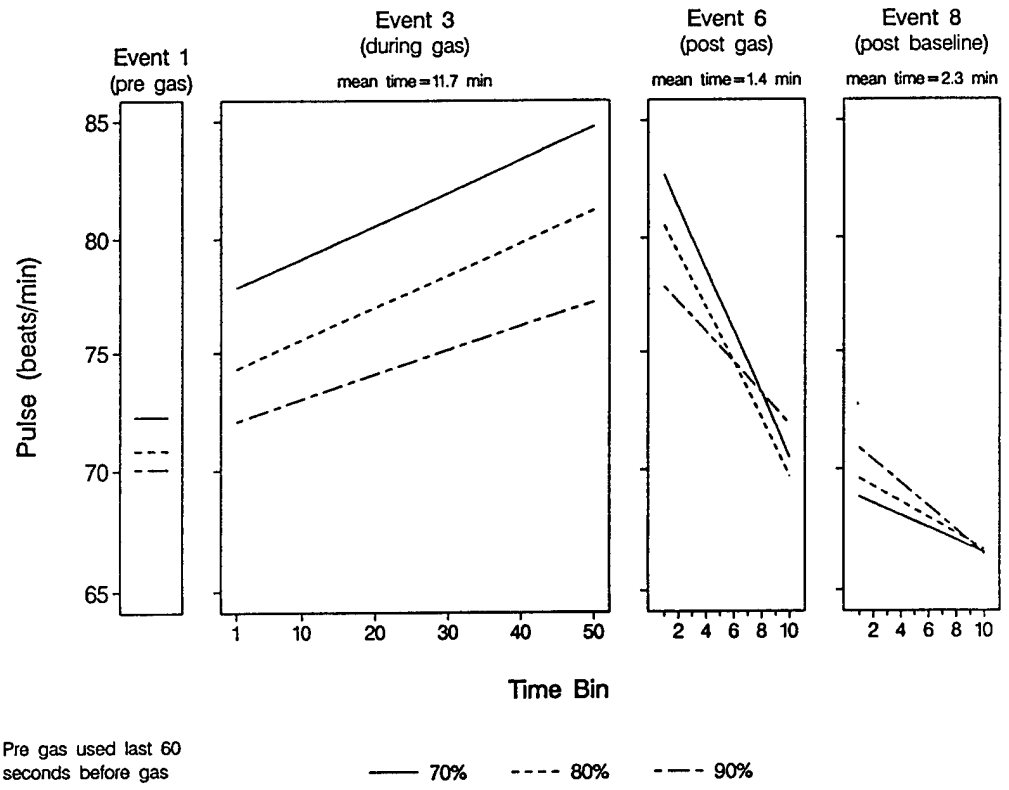


Figure 7. Averaged Regression Lines for Prebaseline (Event 1), Desaturation (Event 3), Resaturation (Event 6), and Postbaseline (Event 8) for Pulse.

## Performance Findings

All subjects required at least three days of practice runs to meet the minimum performance criteria sited in Methods.

Performance as measured by reaction time did show a trend towards longer reaction times (RT) between the prebaseline task (Task #1) and the task following desaturation (Task #2), and between the prebaseline (Task #1) and postbaseline tasks (Task #3). However, the trends

were not consistent. For example, there was a greater change in RT at 80% desaturation than at 70% desaturation, and there was no demonstrable difference in the changes between the 70% desaturation RTs and the 90% desaturation RTs. There were no significant differences in RTs between any of the conditions, nor between gas mixes. Error rates showed no significant changes.

## Evoked Potential Findings

Measurements of event-related P300s were consistent with the classic oddball paradigm. Analysis showed significantly higher P300 amplitudes for the target set than the non-target set across all task conditions ($F(2,36)=53.15$, $p=.0001$), across all gas mixes ($F(2,36)=47.99$, $p=.0001$), and at all scalp loci ($F(2,36)=44.21$, $p=.0001$). There was no significant difference found in P300 latency between the target versus non-target sets. This verification of the oddball paradigm tends to increase the validity of the following target condition P300 data.

The P300 amplitudes and latencies at each task condition are represented graphically for each gas mix (listed by target saturation) in Figure 8 (for 90%), Figure 9 (for 80%), and Figure 10 (for 70%).

The target P300 amplitudes for the 90% gas mix tests were not significantly different at any of the scalp sites (Cz, Pz, Oz) across the test conditions (prebaseline to

desaturation to postbaseline tasks). The P300 latency at the Cz site, however, was significantly longer at prebaseline than at desaturation ($t=27.52$, $p=.0001$), or at prebaseline than at postbaseline ($t=12.80$, $p=.0003$).

During the 80% gas mix runs, the target amplitude was not found to be significantly different between the prebaseline and desaturated conditions, but was significantly lowered between the prebaseline and postbaseline conditions at the Cz and Pz sites (Cz: $t=5.39$, $p=.0490$; Pz: $t=7.36$, $p=.0239$). The latency increased from prebaseline to desaturation at the Cz site ($t=9.12$, $p=.0081$), and from prebaseline to postbaseline at the Cz site ($t=13.16$, $p=.0001$).

During the 70% gas mix runs, the same pattern as with the 80% mix runs was seen. There was no significant difference between the amplitudes of the prebaseline and desaturated conditions at any electrode site, but was significant for prebaseline versus the postbaseline at the Cz site ($t=7.84$, $p=.0200$). The latency also increased from prebaseline to desaturation, and from prebaseline to postbaseline at the Cz site (Pre vs Desat: $t=25.13$, $p=.0001$; Pre vs Post: $t=20.96$, $p=.0001$).

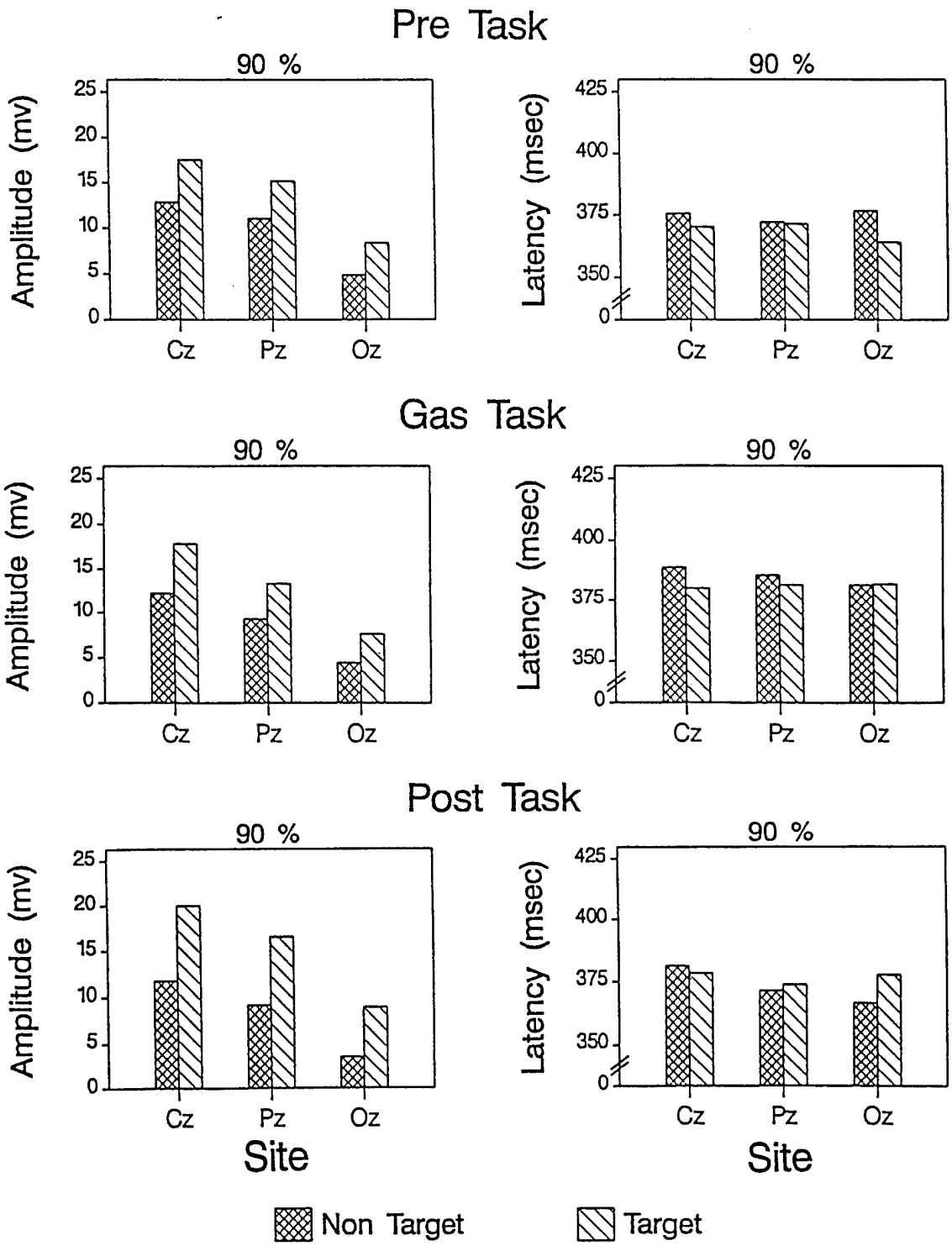


Figure 8. Target P300 Amplitudes and Latencies for each Test Condition for the 90% Mix

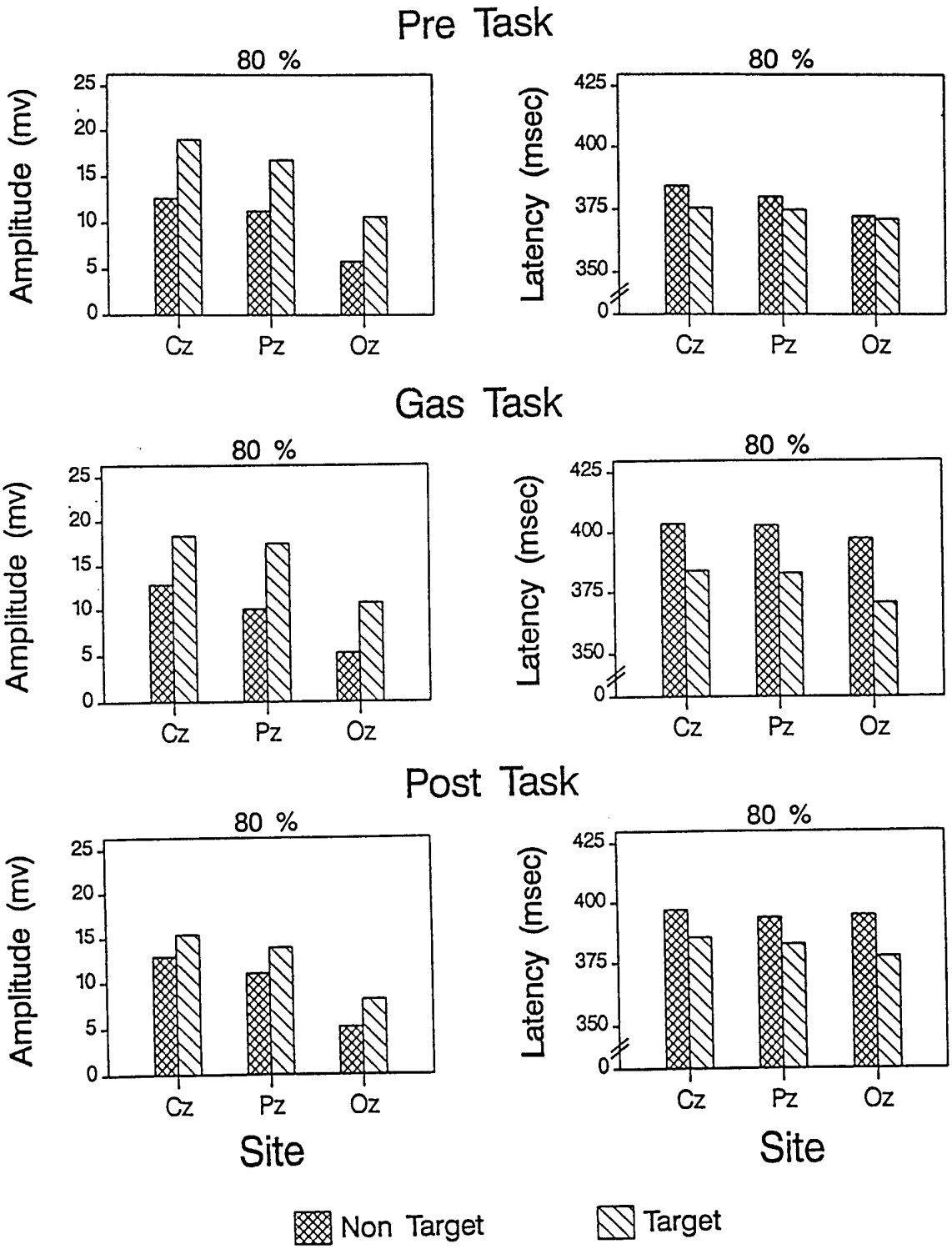


Figure 9. Target P300 Amplitudes and Latencies for each Test Condition for the 80% Mix

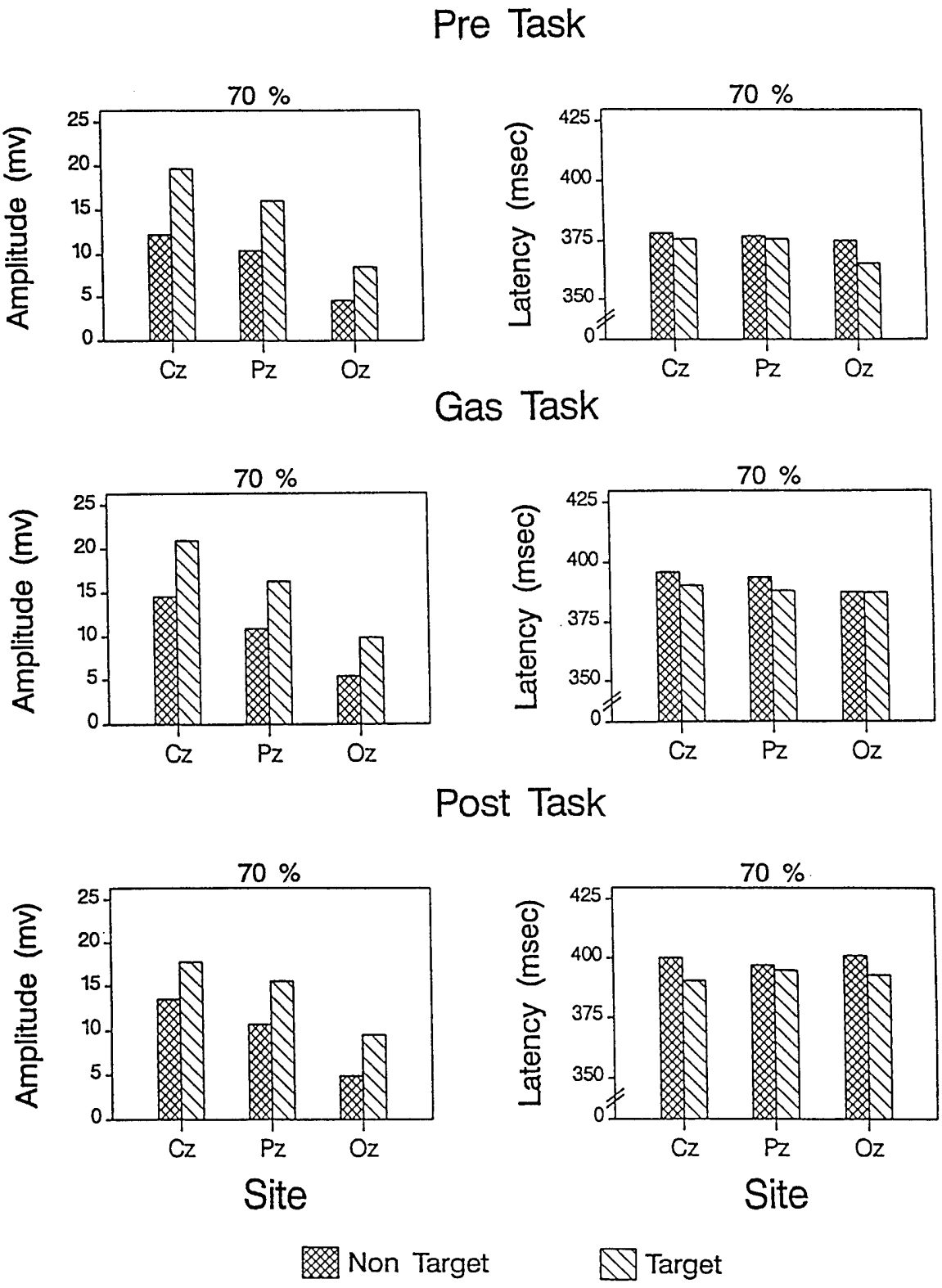


Figure 10. Target P300 Amplitudes and Latencies for each Test Condition for the 70% Mix

# DISCUSSION

## Oximeter Performance

The prebaseline arterial saturations of all subjects on air were well within the normal range of 98 to 100%, which lessens the possibility of instrument error in other SaO2 readings. It also serves to validate the preauricular sensor position as an acceptable site.

The prebaseline sample population average rSO2 of 64.39% and standard deviation of 3.62%, compared very well with other reported population averages. McCormick et al. (1991) reported a study of seven subjects, with a mean rSO2 of 64%, with a standard deviation of 3.4%[32]. In a larger study of 100 randomly selected subjects, Dujovny et al. (1992) reported a mean rSO2 of 68.6% +/- 5.6.[19] Only one subject was outside two standard deviations (although within three). In this case, the subject was an African-american male. Zeballos and Weisman (1991) have reported that in black subjects oximetry results in lower readings than that of arterial blood samples during exercise at simulated altitude, although the trends were still valid.[33] Skin pigmentation may influence photospectrometric readings, since it is a significant chromophore that can reduce reflectance, so this is not a surprising finding. In an

uncompleted study performed by the author to find normal population rSO2 values, it was found that African-americans tended to have rSO2 values averaging 7% lower than the average of lighter skinned people in 70 subjects examined.[34] Dujovny et al. (1992), in the study mentioned above, found a 5% lower average rSO2 among dark skinned individuals, with p=.0078.[19] This does not invalidate oximeter readings in highly pigmented individuals, but serves to caution one against using absolute saturation values. Certainly trends can still be followed. In the clinical setting, a separate set of "normal values" for darkly pigmented patients may be needed, but by no means obviates the technology. Awareness of the potential differences is also necessary in research. As far as the current study, since the subject's rSO2 baseline values were within 3 standard deviations, it was felt unnecessary to exclude his data, and that he simply represented an outlier.

The responses of the rSO2 and SaO2 to the hypoxic mixes were identical through the desaturation and hypoxic plateau. The decreased arterial oxygen levels affect both parameters equally, with the low SaO2 leading to an equally low venous oxygen saturation (SvO2). Both readings are proportionally effected, as represented by the mirror-image slopes.

However, during resaturation the slopes differed significantly. The rSO2 data had failed to return to prebaseline levels despite the rapid return of SaO2 values. The explanation is that the arterial blood is rapidly

reoxygenated from the lungs, while the rSO2 value, with its heavy weighting of venous blood (75%), will still be influenced by increased extraction of oxygen by the hypoxic cerebral tissue. This will result in a lowered venous oxygen saturation value (SvO2), which will remain so until the cerebral tissue has completely recovered. This lowered SvO2 will result in the rSO2 value remaining low as well. Therefore the rSO2 may more accurately characterize cerebral oxygen status than SaO2.

## Heart Rate Response

The heart rate responses seen during the study are consistent with previously described and well-known compensatory mechanisms seen in response to hypoxia.[35] This is exemplified by the significant increase in heart rate during the desaturated conditions. The observed trend of lower postbaseline than prebaseline values can be interpreted as related to pre-run anxiety. The difference though was not significant, thereby only representing a rapid return of pulse towards prebaseline levels.

Even though there was a significant increase in the heart rate during the desaturated conditions for all gas mixes, there was no significant difference between any of the gas mixes at each condition, despite a trend for greater heart rate for greater hypoxia (see Table 4). Essentially then, the heart rate responded the same to any level of hypoxia.

A contradiction to this, though, can be found in analysis of the slopes of heart rate response to the three gas mixes. There was significance, but only during resaturation. Since there was rapid convergence of the heart rate to the baseline level, this difference among resaturation slopes represents the more rapid return to normal from the deeper hypoxia, and a slower return to normal of the less profound hypoxia. This therefore seems to magnify the insignificant but obvious trends of greater pulse at desaturation discussed above. This would be a very difficult response to measure in real-time, and is of limited validity given the insignificance of the heart rate data.

Therefore, at least as far as the findings of this study represent, heart rate has no predictive value for the severity of hypoxia. Correspondingly, pulse rate is not a useful measure to predict performance deficit in hypoxic conditions.

## Performance

The subject's learning curves were generally plateaued after three days of practice. A few required more to meet the criteria of 20 milliseconds between tests, and one error per test. There was agreement between the last practice averages and the prebaseline task RTs and error rates.

The reaction time data did not prove significantly different for any of the gas mixes nor for any of the task

conditions. Wesensten et al. (1993) have shown significant lengthening of reaction latency (RT) with increasing altitude.[36] They were studying long term exposure though, on the order of hours. Kida & Imai (1993) used shorter exposure times of about 45 minutes to test performance during altitude exposures of from about 3,000 to 6,000 meters.[37] They showed variable individual subject response, with 12 of 38 subjects having no lengthening of RT, even at 6000 meters. It is possible then that the increase in RT is partially time dependent; i.e. the longer the exposure the greater the increase in latency. The relatively short exposure time used in this study, may in part explain why there were no consistent trends or significant differences seen. The error rate was very low, and did not provide any significant trends.

The question of time is a potential problem, in that there was marked variation in the times to desaturation. It is possible that a more uniform gas interval may have altered the findings, as compared to using target SaO2s.

The choice of a one-target memory set was made on the basis of maximizing the P300, with evoked potential measure being the primary measure of performance. The single memory set has the added advantage of low error rates, since a high error rate makes reaction time data more difficult to interpret.[38] It has been suggested that memory sets of one not be used[29], but the previous advantages outweighed this recommendation.

The results of P300 analysis were consistent with the oddball paradigm, and serves to validate the event-related evoked potentials seen.

The better performance at 90% by the subjects suggests that they were "recovering" from the desaturation more quickly, with less CNS impact than they did with the more hypoxic mixes. For the 70% and 80% gases, the target P300 amplitude decreased and the latency increased and remained so through recovery of SaO2.

This finding correlates with the failure of the rSO2 to return to normal, suggesting that rSO2 may be a more accurate predictor of CNS function and performance, at least as far as supported by target P300 evoked potential EEG data.

## Comparison of Gas Mixes

A consistent pattern across the data presented was that no significant difference was seen between the 70% target saturation mix and the 80%, but that these both differed from the 90% mix. This tendency was seen with the following data.

The time to desaturation showed no statistical difference between 70% and 80%, with significance present between them and 90%.

The data for time to resaturation was not globally significant, but pairwise t-test comparisons done as a matter of course did not show any significant difference

between the 70% and 80% mixes, while demonstrating significance difference of both from the 90% mix.

Pairwise comparisons of the rSO2 slopes during desaturation across the gas mixes demonstrated no significance to the .01 level between 70% and 80%, while there was a significant difference to the .01 level for 70% versus 90%, and 80% versus 90% for the rSO2 slopes.

The 70%-80% comparison for the SaO2 resaturation slope was not significant at the .01 level, while the pairwise comparison with the 90% mix for both was highly so ($p=.0002$ and $p=.0024$ respectively).

A pairwise comparison of the slopes of heart rate response during resaturation failing to show significance between the 70% and 80% mixes.

An examination of P300 amplitude data for target sets at the Cz locus, reveals that the 70% and 80% values mirrors each other markedly well, in distinction to the 90% values. The latency data also shows the same pattern.

The weight of this evidence indicates that the data acquired from the 70% target mix is essentially a duplicate of that of the 80% target mix. In future studies of this type examining performance at simulated altitude it would therefore be reasonable to eliminate the 80% mix. This would serve two purposes: one, reduce duplication, and two, using the 70% mix for comparison with 90% would serve to minimize any potential Type II error that could be present with the 80% mix.

# CONCLUSIONS

This study served to validate the proposed combination of cerebral oximetry, simulated altitude and performance testing in a system that could be utilized in a centrifuge.

While the Somanetics INVOS 3100 derived rSO2 readings correlated well with the SaO2 values during desaturation, the slower return of the rSO2 towards a normal baseline during resaturation paralleled the failure of post-hypoxia performance to return to baseline. Although this study did not follow performance until a return to normal, the correlation of cerebral regional oxygen saturation with post-hypoxia performance is superior to that of systemic arterial saturation. Therefore, rSO2 may offer improved prediction of altitude-induced performance deficit.

The Psychophysiologic Assessment Test System provided a effective and convenient means of formatting performance tasks, administering them and simultaneously recording physiologic data. Software changes (already planned) will serve to make the system more user friendly and efficient, especially in the post-test analysis phase.

The 12.8% and 10.9% oxygen/nitrogen mixes (target SaO2s of 90% and 70% respectively), were sufficiently different in most of the study parameters to serve as mild and moderate

hypoxic mixes respectively. The 11.8% mix (80% target SaO2) was not significantly different from the 10.9% mix (70% target SaO2) to warrant its continued use in simulated altitude studies of this nature.

**APPENDIX A**
CONSENT FORM

INFORMATION PROTECTED BY THE PRIVACY ACT OF 1974

TITLE: Performance Effects of Decreased Cerebral Tissue Oxygen Saturation Induced by Various Levels of Mixed $O_2/N_2$.

1. a. Nature: This study will validate the Physiological Assessment Test System (PATS) and Somanetics INVOS 3100 Cerebral Oximeter in a reduced oxygen environment. In addition to the validation of these systems, pulse oximetry will be employed to further our understanding of the relationships between cerebral and arterial oxygen saturation in a controlled hypoxic environment.

b. Purpose: The purpose of this study is to implement a standardized means of validating the PATS and INVOS systems to speed their implementation into centrifuge research.

c. This program will run for approximately 2-3 months, during which time data collection will take place followed by subsequent statistical analysis.

2. As a member of the Sustained Acceleration Stress Panel you are invited to participate in a hypoxia study involving mixed gas (decreased oxygen balanced with nitrogen). This study will evaluate two separate physiological monitoring systems (the PATS and INVOS 3100). The PATS is specifically designed to run performance tasks and collect various physiological data, electroencephalogram (EEG), eye blink, and heart rate. This study will specifically evaluate EEG and performance task generation. In addition, cerebral and arterial oxygen saturation data will be obtained non-invasively using the INVOS 3100 and the Nellcor N-200 oximeters.

The Somanetics INVOS 3100 is an investigational device, of non-significant risk, which non-invasively measures the regional oxygen saturation of brain tissue through the scalp and skull. It measures infrared and near-infrared light, from an LED (light-emitting diode) contained on a self-adherent sensor which is placed on the skull.

Our current understanding of the mixed gas technique is that decreased mixtures of oxygen mixed with a remaining amount of nitrogen have been used to simulate the partial pressure of oxygen at altitude and therefore to bring arterial oxygen saturation to well controlled hypoxic levels. The simulated altitudes proposed in this study include: 13,000, 15,000, and 17,000 ft.

Subject Signature/SSN_____Date_____

You will be asked to complete orientation training of a simple performance task which involves memorizing a letter and accurately choosing the letter from a subset of letters being presented on a monitor in front of you.

In the experimental phase, instrumentation will include three lead EEG using wet electrodes, arterial oxygen saturation, and cerebral oxygen saturation leads using self adhering near-infrared and infrared LED oxisensors. You will be requested to breath one of four mixed gas conditions (10.9, 11.8, 12.8% $O_{2P}$ with the remaining component nitrogen, and an ambient air condition). The first three will produce a mild to moderate hypoxic state. In all test conditions where oxygen mixtures are less than 20.8% $O_2$, decreases in blood oxygen saturation will occur. You will continue to breath the gas mixture for no longer than 30 minutes and then be returned to ambient air. There will be six separate sessions, on different days, so you will experience each of the three gas mixes twice. The first set will be for "blend" purposes (to accommodate you to the full procedure), and the final three for "data" purposes.

3. Experimental Risk:

a. Historically, the physiological effects and symptoms of hypoxia exist only during the hypoxic exposure and resolve once breathing ambient air. These symptoms include: increased breathing rate, cyanosis (blue coloration of skin), confusion, poor judgment, loss of coordination, and unconsciousness, as well as behavioral changes, such as elation or belligerence, which may be noted by the individual and/or investigator. Subjective symptoms may include: breathlessness, apprehension, headache, cold & hot flashes, blurred/tunnel vision, numbness or tingling.

4. You are not expected to benefit directly from this participation. It may be of interest to you to experience first hand the effects of hypoxia. A possible indirect benefit will be that, as a subject, you may contribute to acceleration experiments that will benefit the USAF.

5. Alternative methods of validating this equipment, such as mathematical models or the use of lower primates, would not in most cases yield conclusive data. Human subjects also must be used.

6. I, _____, am participating because I want to. The decision to participate in this research study is completely voluntary on my part. No one has coerced or intimidated me into participating in this program.

Subject Signature/SSN_____Date_____

_____ has adequately answered any and all questions I have asked about this study and my participation, and the procedures involved, which are set forth above, which I have read. I understand that the Principal Investigator or a designee will be available to answer any questions concerning procedures throughout this study. I understand that if significant new findings develop during the course of this research which may relate to my decision to continue participation, I will be informed. I further understand that I may withdraw this consent at any item and discontinue further participation in this study without prejudice to my entitlements. I also understand that the Medical Monitor for this study may terminate my participation in this study in he/she feels this to be in my best interest. I may be required to undergo certain further examination, if in the opinion of the Medical Monitor, such examinations are necessary for my health or well being.

7. I have considered and accept the unlikely but theoretical possibility of the following:

(a) If physical exams and/or monitoring of physical parameters related to this experiment are conducted, it is possible for an unknown physical defect to come to light which might result in disqualification from flight or other special duty.

(b) If physical injury were to occur it could result in physical disqualification from flight or other special duty.

8. I understand that my entitlement to medical care or compensation in the event of injury is covered by federal laws and regulations, and that if I desire further information I may contact Mr. Lloyd Tripp of CFBS, the principal investigator of the parent project.

9. I understand that for my participation in this project I shall be entitled to payment as specified in the DOD Pay and Entitlements Manual or in current contracts, or I understand that I will not be paid for my participation in this experiment.

10. I understand that my participation in this study may be photographed, filmed or audio/videotaped. I consent to the use of these media for training purposes and understand that any release of records of my participation in this study may only be disclosed according to federal laws, including the Federal Privacy Act, 5 5 U.S.C. 552a, and its implementing regulation. This means personal information will not be released to an unauthorized source without my permission.

Subject Signature/SSN_____Date_____

11. **I FULLY UNDERSTAND THAT I AM MAKING A DECISION WHETHER OR NOT TO PARTICIPATE. MY SIGNATURE INDICATES THAT I HAVE DECIDED TO PARTICIPATE HAVING READ THE INFORMATION PROVIDED ABOVE.**

Volunteer
Signature_____Date_____

Volunteer SSN_____

Witness
Signature_____Date_____

Principal Investigator
Signature_____Date_____

Principal Investigator

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INFORMATION PROTECTED BY THE PRIVACY ACT OF 1974

Authority: 10 U.S.C. 8012, Secretary of the Air Force; powers and duties; delegation by; implementation by DOE 12-1, Office Locator.

Purpose: is to request consent for participation in approved medical research studies. Disclosure is voluntary.

Routine use: Information may be disclosed for any of the blanket routine uses published by the Air Force and reprinted in AFP 12-36 and in Federal Register 52 FR 16431.

## APPENDIX B
The Effect of Frontal Sinus Size on the Somanetics Invos 3100 Oxisensor.

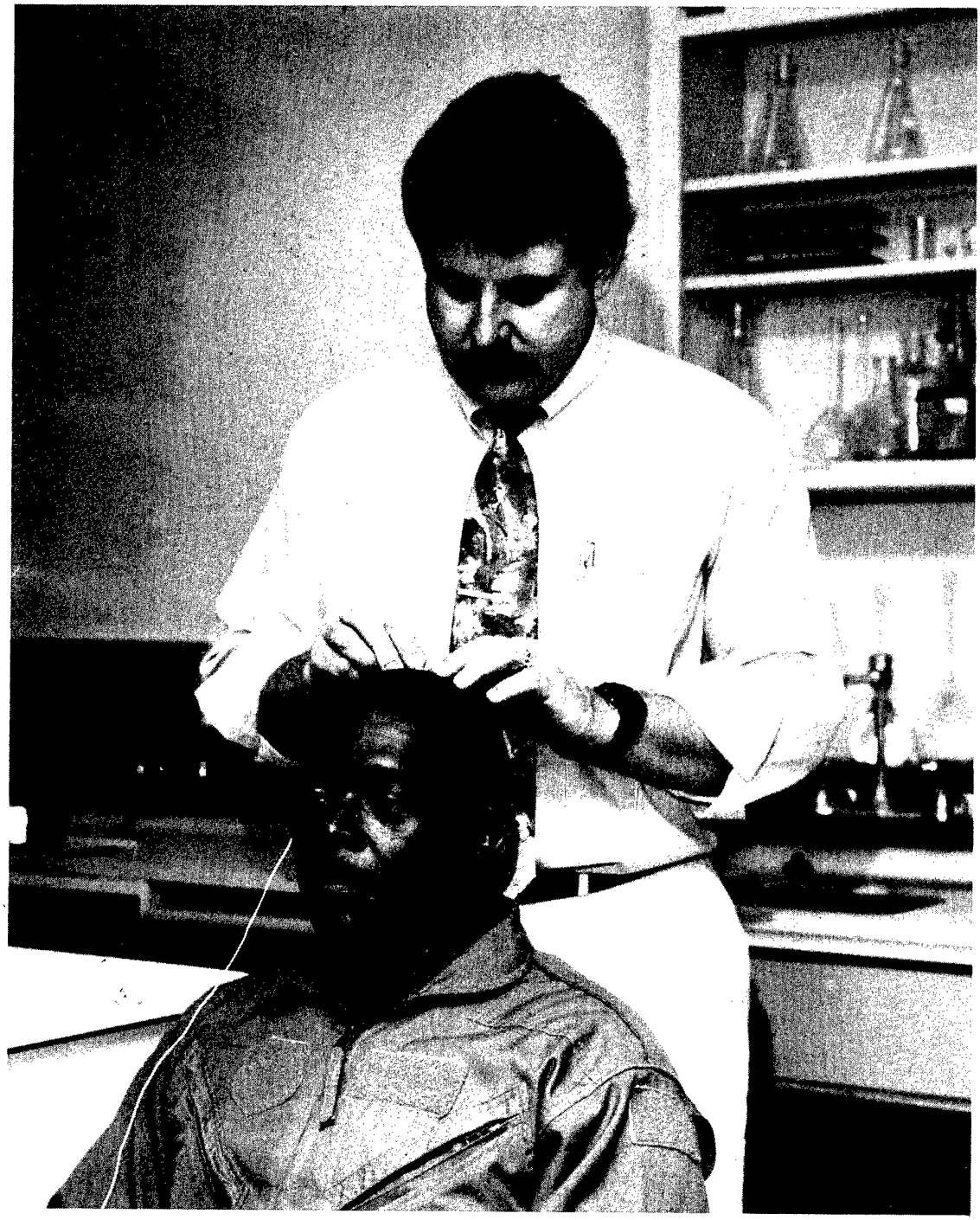
Of concern in signal integrity is the potential problem of the frontal sinuses. Instructions on application of the sensor from Somanetics state that the frontal sinuses must be avoided by placing the sensor as far up the forehead as possible, while still avoiding the hair.[25] It is felt that the signal reflected back to the sensor will not be representative of cerebral tissue, having to traverse an air pocket as well as having to traverse a greater depth to the cortex (R. Kasperski, Somanetics Corporation, personal communication, August 1993). These combine to give a reading that reflects the bone and soft tissue surrounding the frontal sinuses, and not of the target brain tissue.

This can be a problem due to the great variability among individual frontal sinus dimensions. Gray's Anatomy lists average measurements as 3 cm in height, 2.5 cm in width, and 2.5 cm in depth.[38] There would therefore be adequate sensor spacing for the "average" patient, but still leaves doubt as to the amount of variation that would be seen.

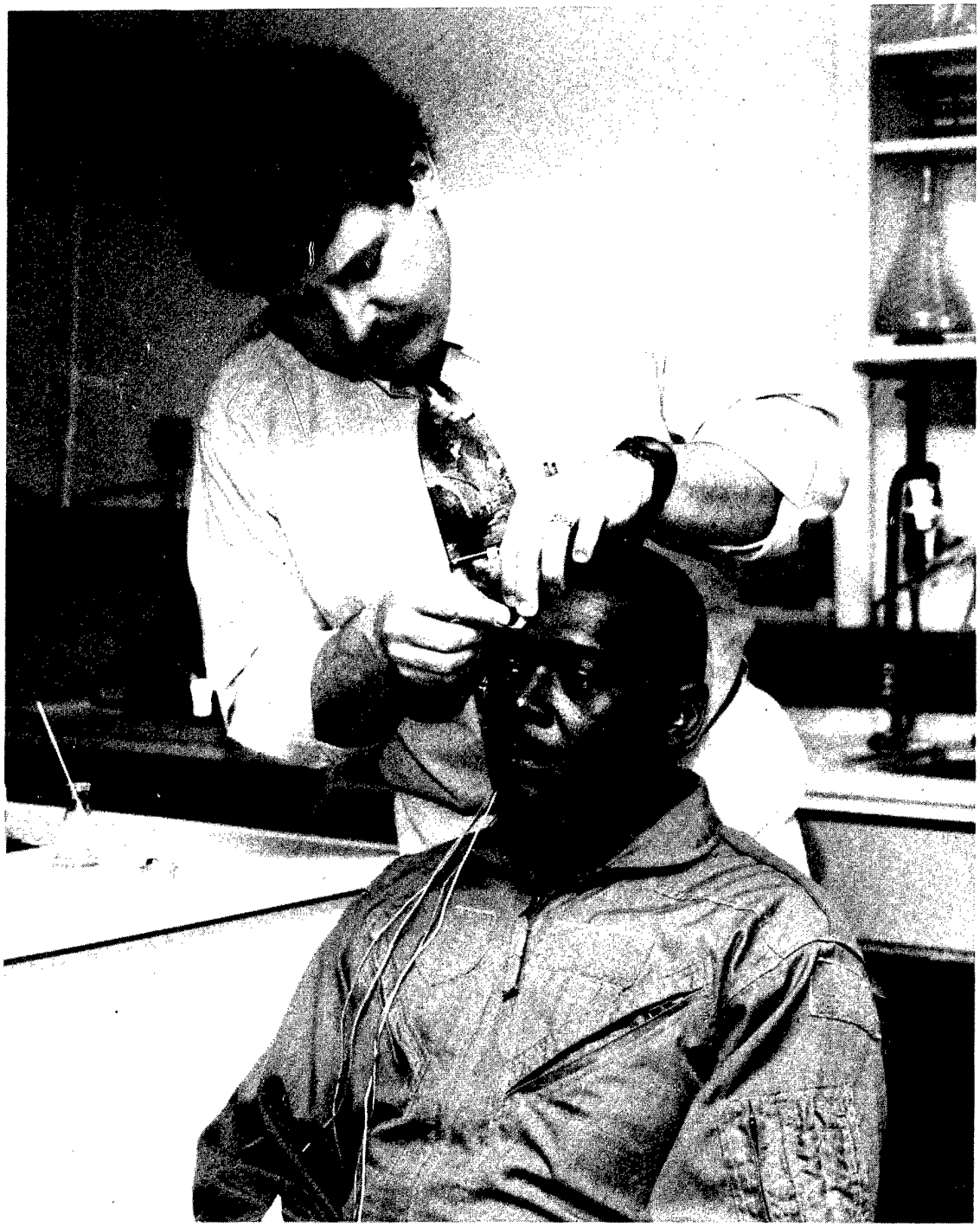
Urken et al used 100 individuals to radiographically demonstrate that the average frontal sinus excursion superior to the superior orbital ridge had a range of 0 to 56.2 mm for the left and 0 to 53.6 mm for the right. The average was 18.5 mm for the left and 18.2 mm for the right, with standard deviations of 11.8 and 10.5 respectively.[39]

Using these figures, about 95% of subjects can be expected to have the superior extent of the frontal sinus to no more than 4.2 cm on the left and 3.9 cm on the right, which should put them below the level of a properly placed INVOS sensor. Given the marked variability in individual size though, both of sinus and forehead, for any serious clinical situation it would probably be prudent to perform translumination of the frontal sinuses prior to use of the INVOS 3100. Translumination of the frontal sinuses is an easy and quick method to assure that placement of the sensor will be appropriate.

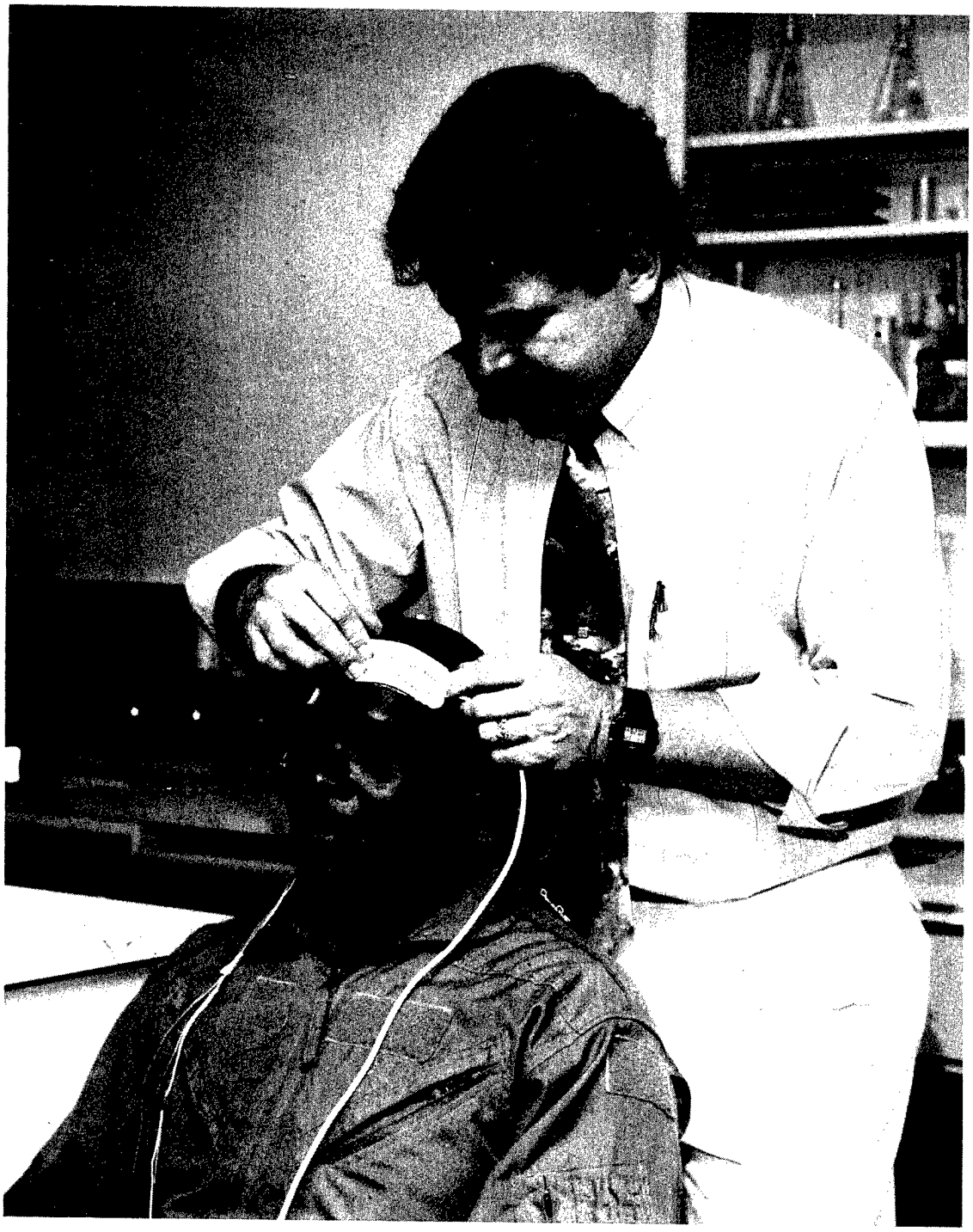
APPENDIX C
Applying EEG Electrode at Cz



APPENDIX D
Applying EOG Electrode

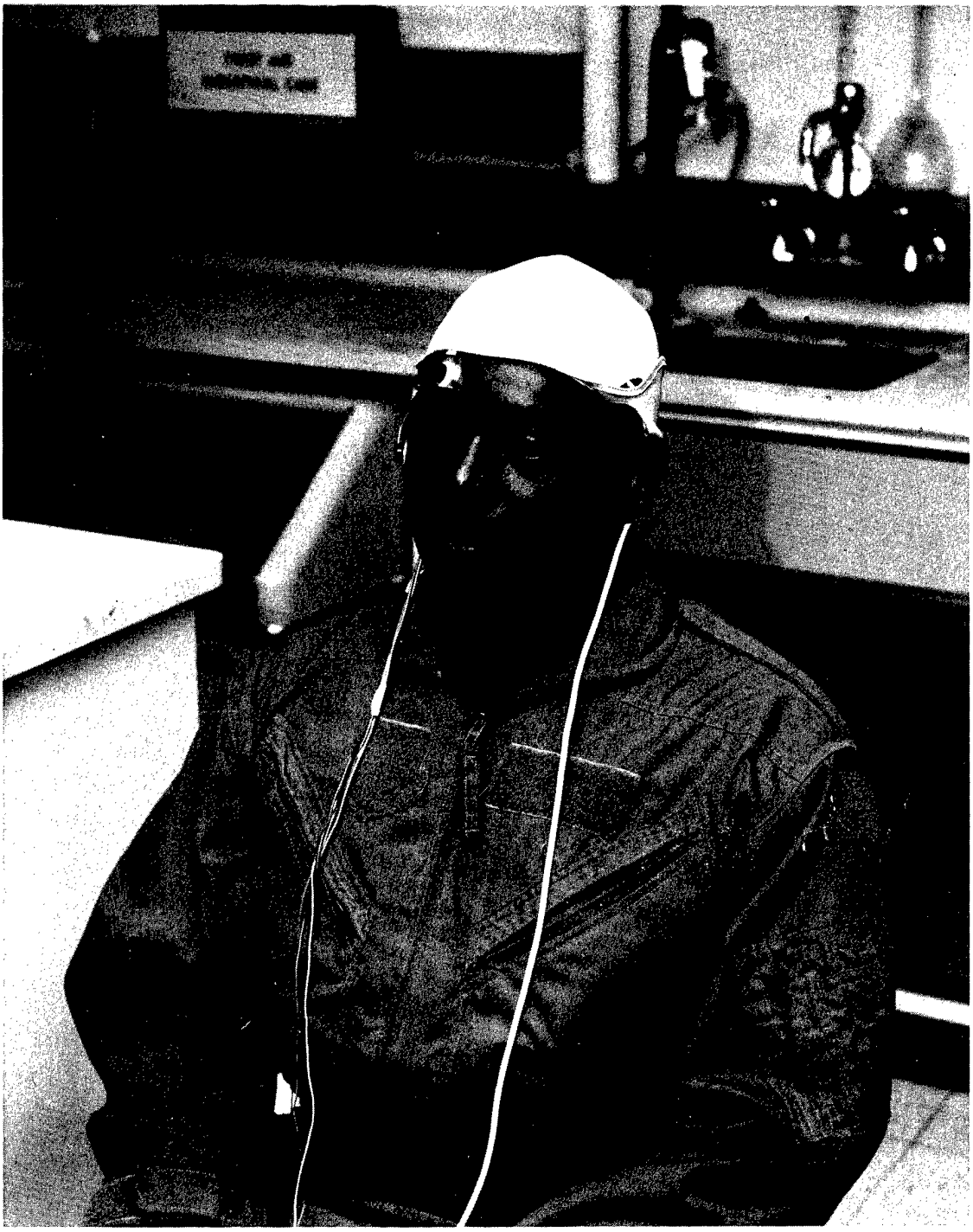


APPENDIX E
Applying Somanetics Oxisensor



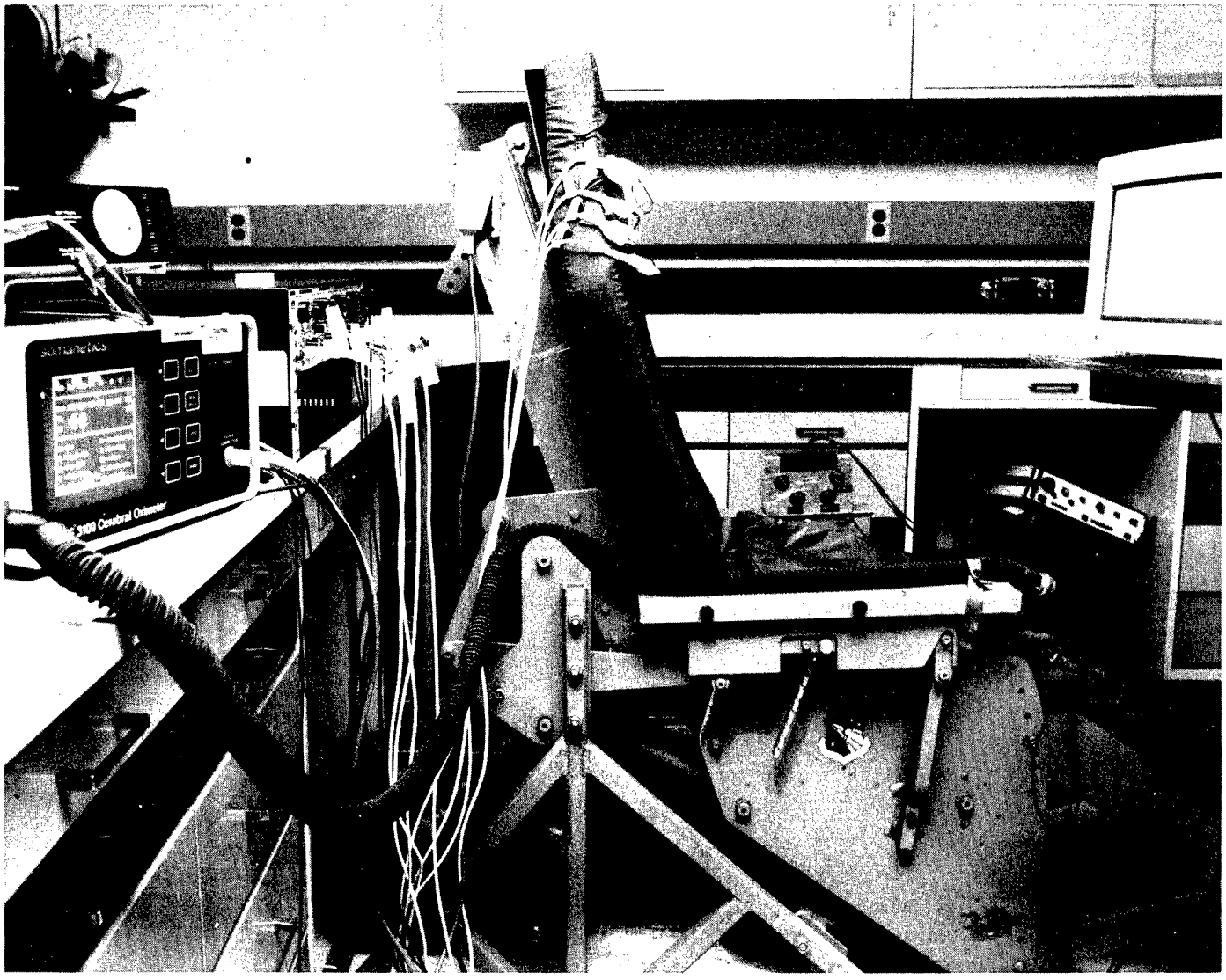
APPENDIX F
EEG Electrode Placement

APPENDIX G
All Leads in Position, with Skull Cap



APPENDIX H
Fully Instrumented Subject
Seated in Test Station

APPENDIX I
Test Station with Seat and Screen
Somanetics INVOS 3100 Cerebral Oximeter on Left



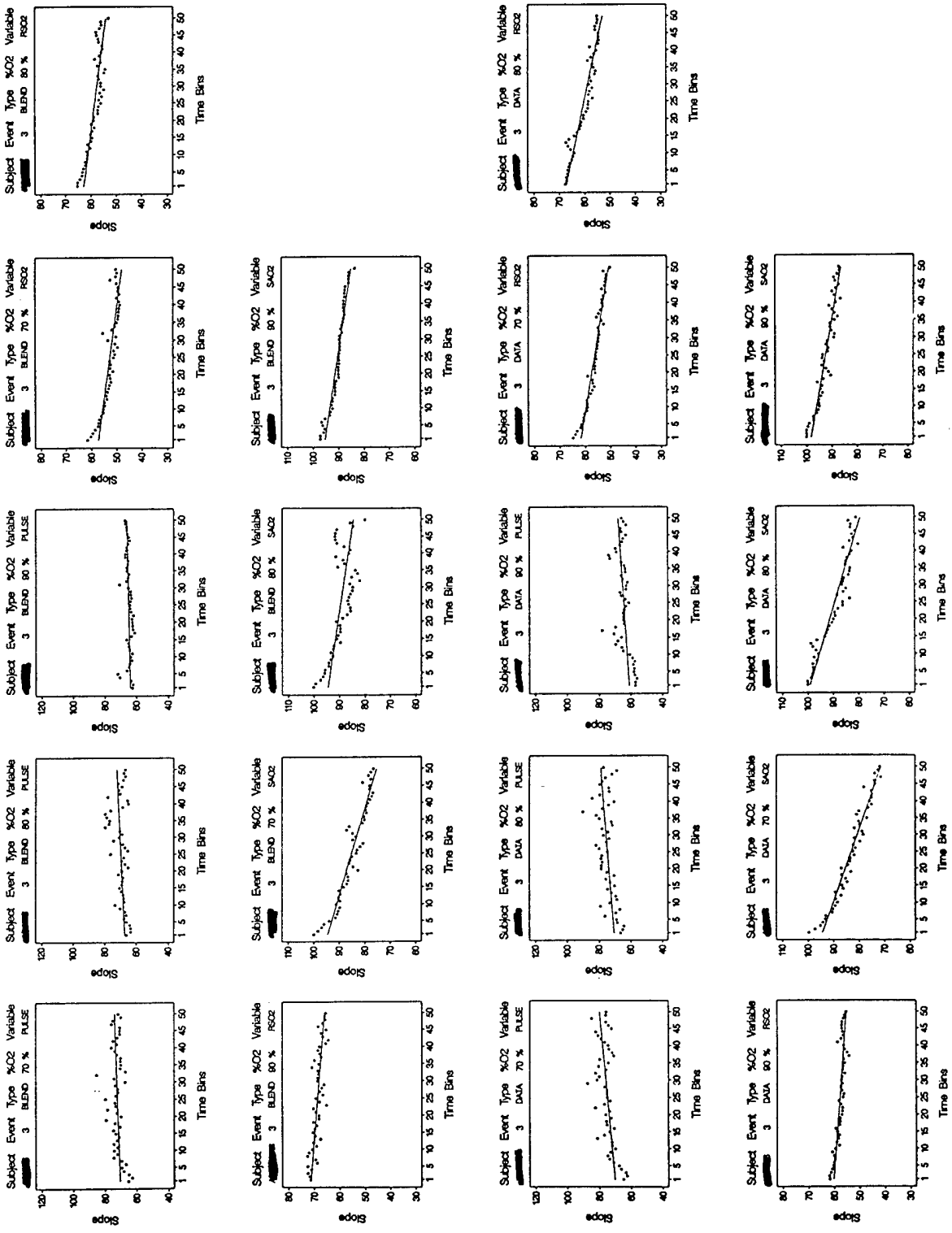
APPENDIX J
Laboratory Set-up with PATS in Right Foreground
Saturation Computer on Left

**APPENDIX K**
Prebaseline Saturation Findings

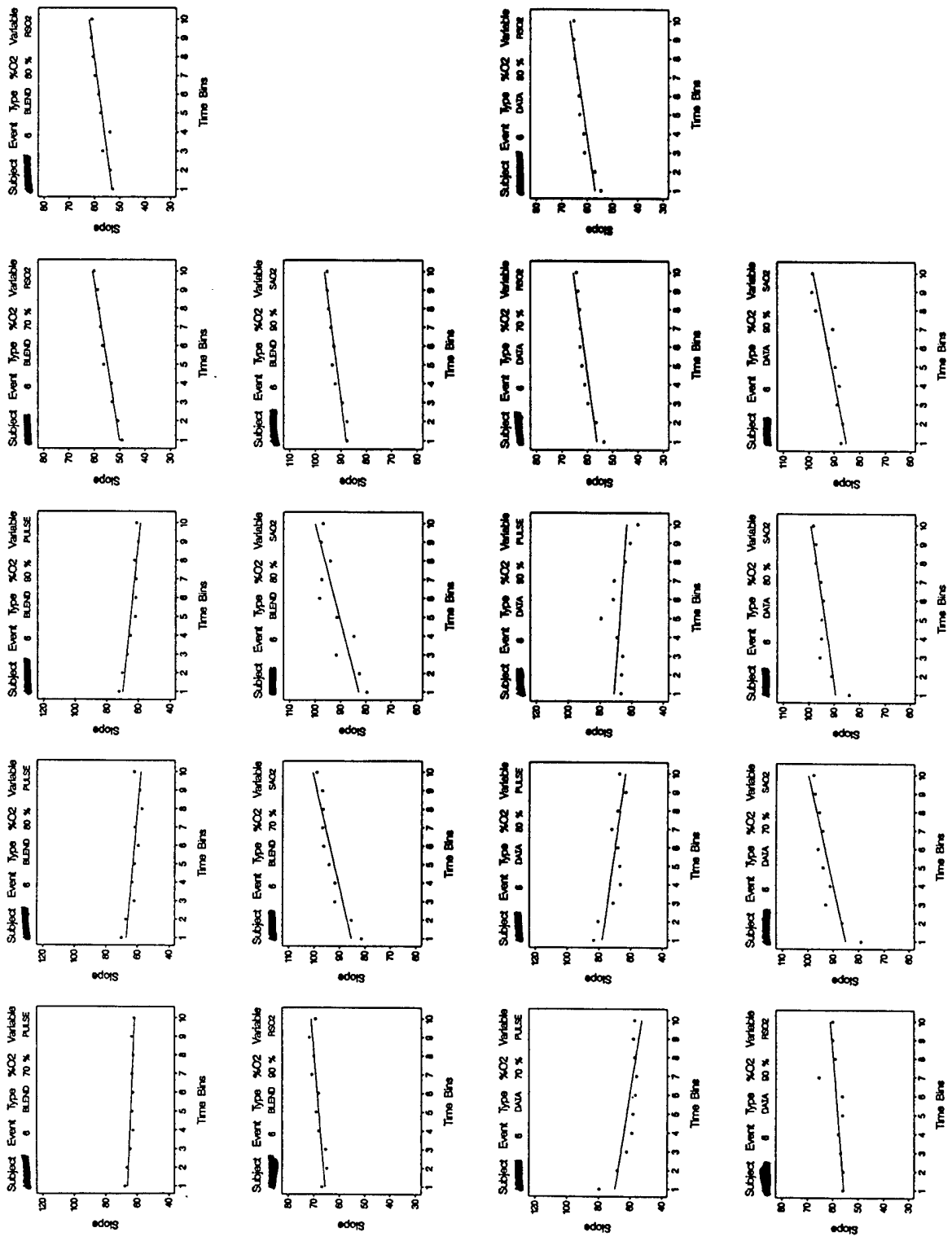
| | BLEND RUNS (Average) (Std. Dev.) | | DATA RUNS (Average) (Std. Dev.) | | ALL RUNS (Average) (Std. Dev.) | |
|---|---|---|---|---|---|---|
| SUBJ | SAO2- | RSO2- | SAO2- | RSO2- | SAO2- | RSO2- |
| 1 | 98.57 | 66.05 | 100.00 | 64.47 | 99.42 | 65.26 |
| | 2.24 | 5.01 | 0.07 | 2.49 | 1.70 | 3.64 |
| 2 | 97.37 | 68.41 | 99.11 | 68.60 | 98.24 | 68.50 |
| | 1.93 | 4.52 | 0.33 | 2.32 | 1.56 | 3.22 |
| 3 | 98.24 | 55.64 | 99.07 | 54.57 | 98.66 | 55.10 |
| | 0.60 | 1.00 | 0.89 | 3.78 | 0.82 | 2.54 |
| 4 | 99.68 | 64.10 | 99.25 | 58.15 | 99.46 | 61.13 |
| | 0.35 | 2.98 | 1.34 | 6.29 | 0.91 | 5.48 |
| 5 | 99.85 | 67.69 | 99.44 | 67.04 | 99.65 | 67.36 |
| | 0.20 | 1.56 | 0.46 | 4.15 | 0.39 | 2.82 |
| 6 | 99.49 | 62.83 | 100.00 | 55.97 | 99.87 | 59.40 |
| | 1.08 | 8.47 | 0.10 | 1.68 | 0.80 | 6.63 |
| 7 | 99.16 | 61.63 | 100.00 | 60.85 | 99.63 | 61.24 |
| | 0.85 | 2.56 | 0.20 | 2.38 | 0.76 | 2.25 |
| 8 | 98.15 | 65.63 | 98.71 | 69.96 | 98.43 | 67.80 |
| | 2.25 | 0.70 | 2.10 | 1.66 | 1.97 | 2.63 |
| 9 | 99.64 | 70.77 | 100.00 | 70.56 | 99.85 | 70.67 |
| | 1.00 | 3.72 | 0.20 | 1.92 | 0.68 | 2.65 |
| 10 | 99.77 | 66.57 | 100.00 | 64.60 | 99.98 | 65.59 |
| | 0.86 | 4.93 | 0.25 | 2.43 | 0.61 | 3.64 |
| 11 | 99.85 | 63.58 | 100.00 | 68.90 | 100.00 | 66.24 |
| | 0.25 | 4.18 | 0.14 | 2.92 | 0.26 | 4.35 |
| AVER. | 99.07 | 64.81 | 99.60 | 63.97 | 99.38 | 64.39 |
| S.D. | 1.06 | 3.60 | 0.55 | 2.91 | 0.95 | 3.62 |
| RANGES | | | | | | |
| MIN | 97.37 | 55.64 | 98.71 | 54.57 | 98.24 | 55.10 |
| MAX | 99.85 | 70.77 | 100.00 | 70.56 | 100.00 | 70.67 |

# APPENDIX L
## Regression Analyses for Individual Subjects

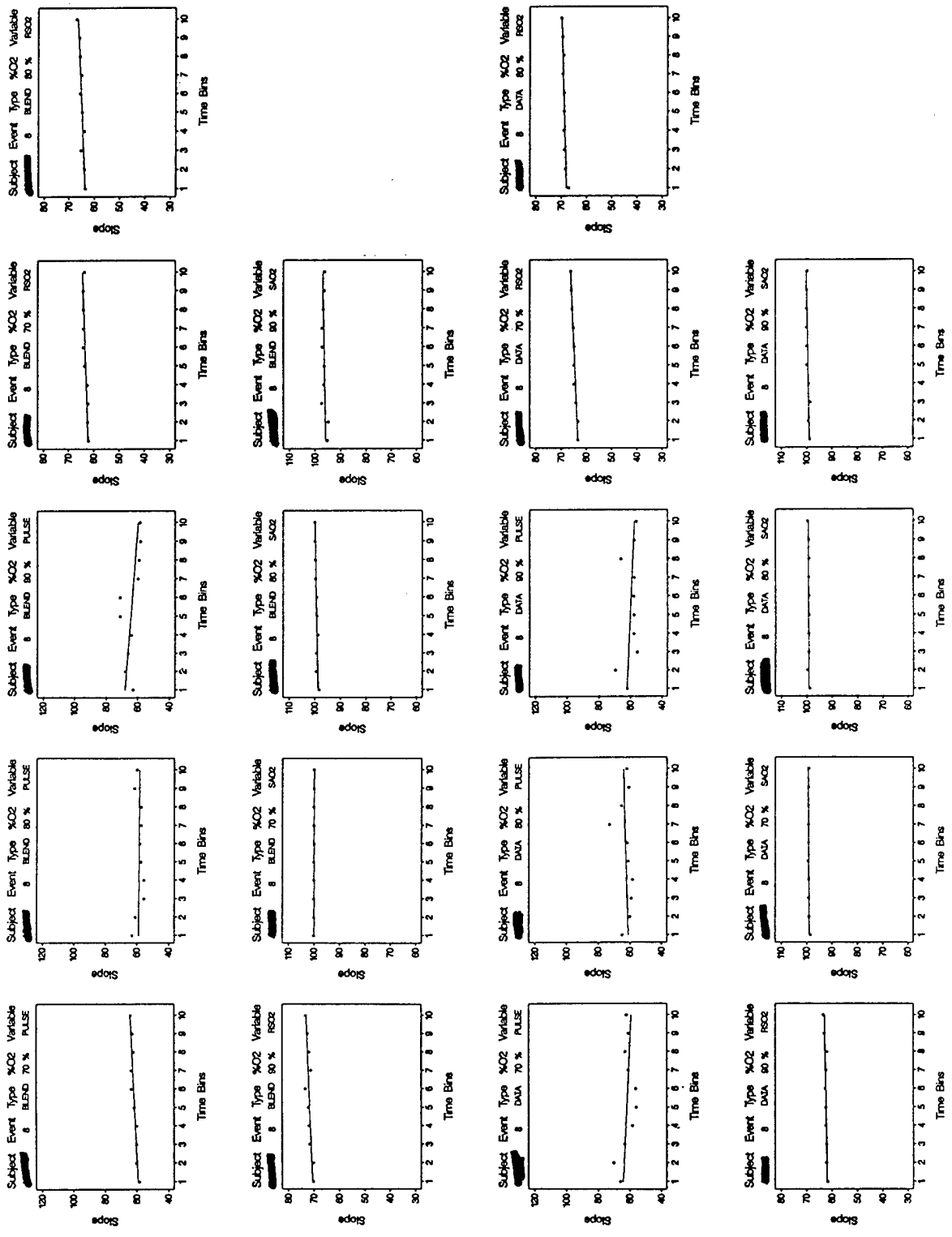
### Subject 1



Subject 1



Subject 1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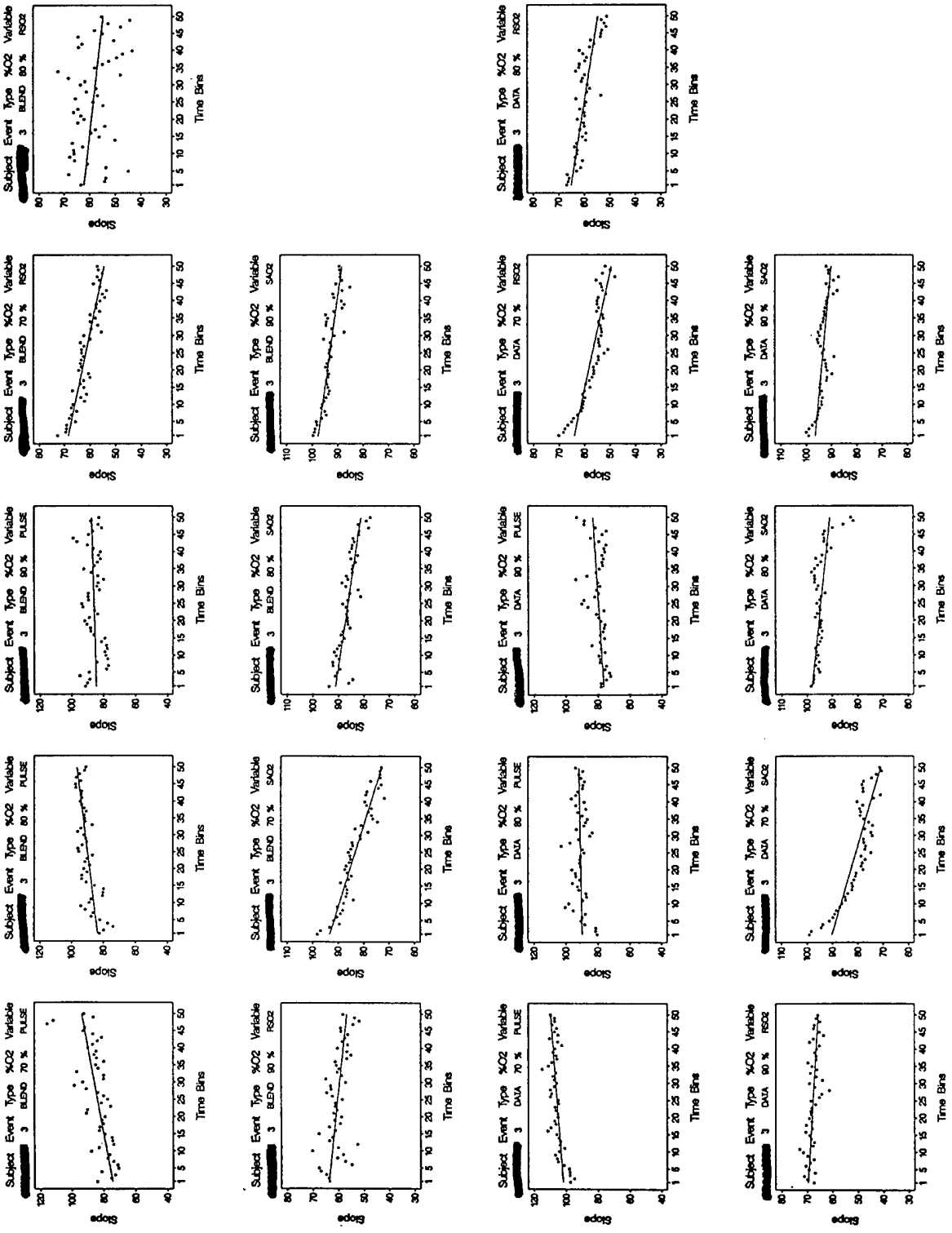
Slope
Time Bins

Subject 2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3 BLEND 80 % SAO2
3 DATA 80 % RSO2
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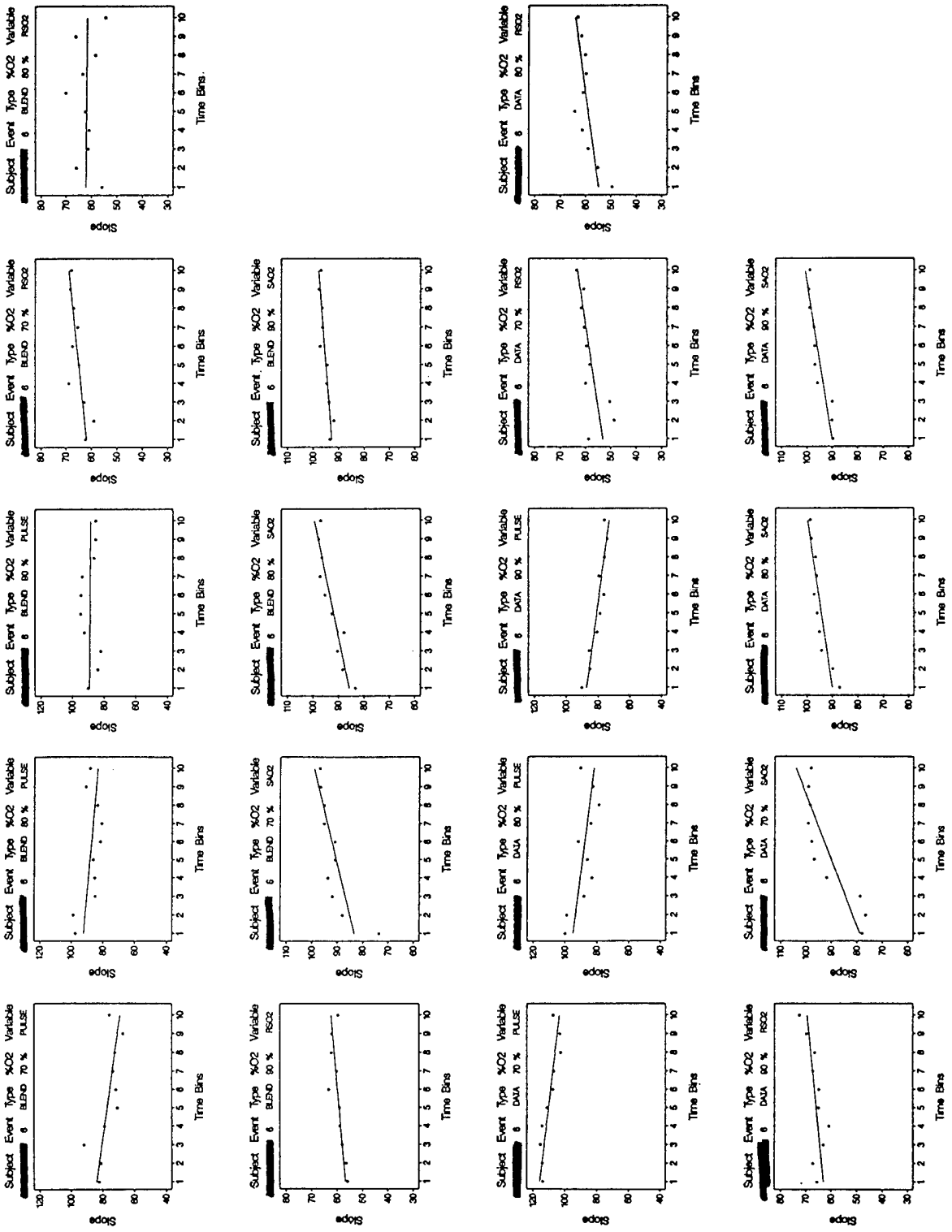
3 DATA 80 % PULSE
3 DATA 90 % SAO2
3 DATA 80 % SAO2
3 DATA 90 % RSO2
Slope
Time Bins

Subject 2



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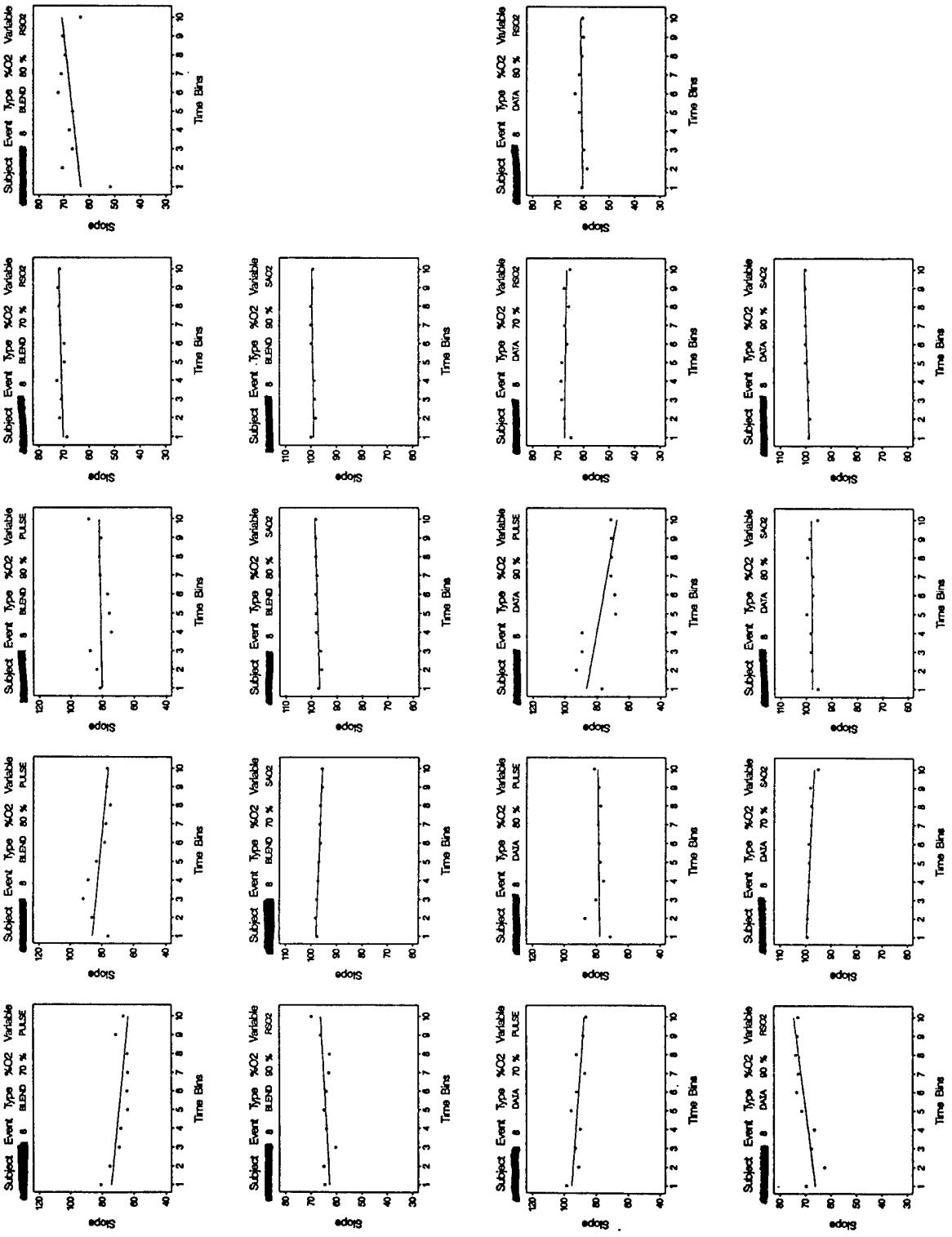
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8 BLEND 70 % PULSE
8 BLEND 80 % PULSE
8 BLEND 70 % SAO2
8 BLEND 80 % SAO2
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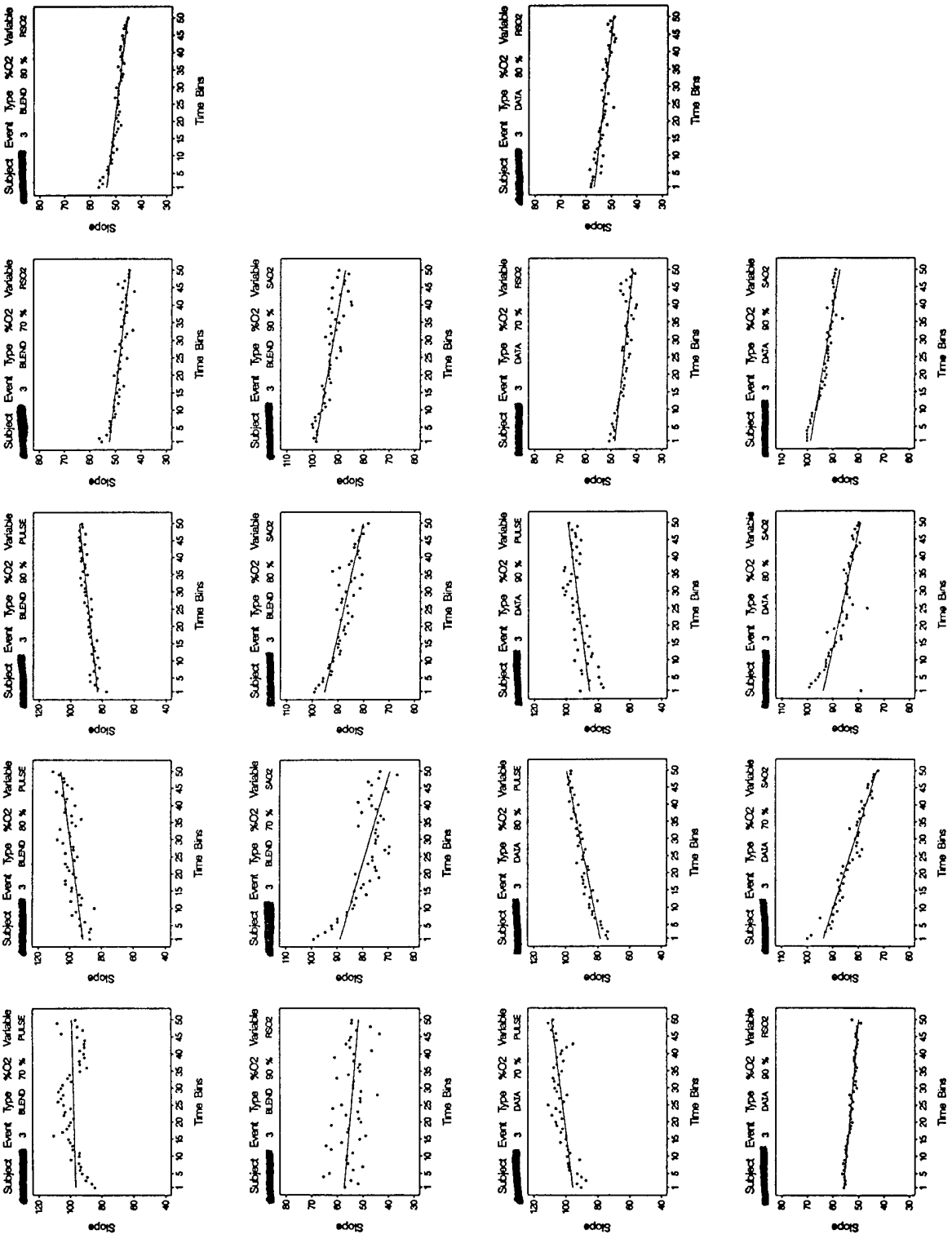
8 DATA 70 % PULSE
8 DATA 90 % PULSE
8 DATA 70 % SAO2
8 DATA 80 % SAO2
Slope
Time Bins

Subject 3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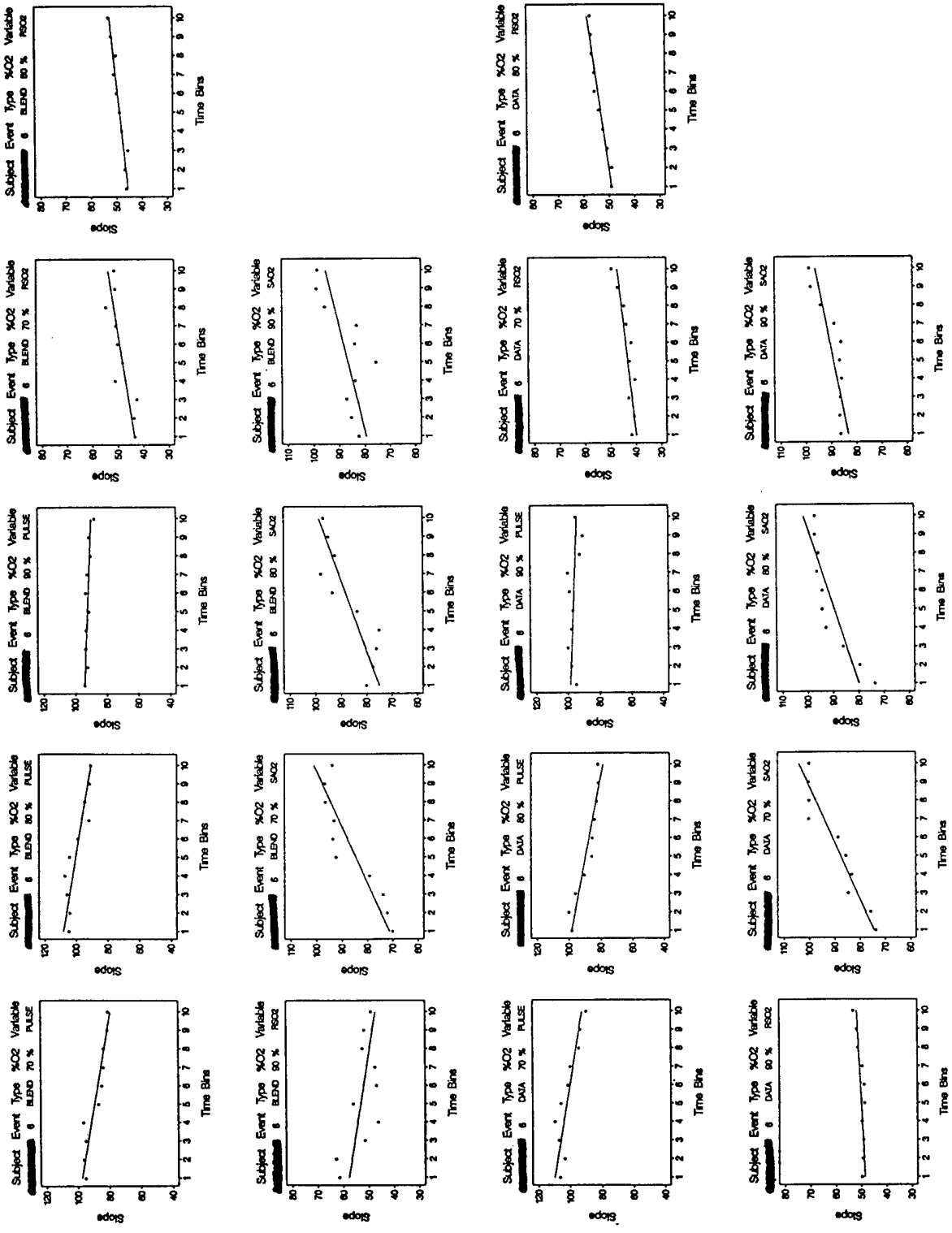
3 BLEND 80 % PULSE
3 BLEND 90 % PULSE
3 BLEND 70 % RSO2
3 BLEND 80 % RSO2
3 BLEND 90 % RSO2
3 BLEND 70 % SAO2
3 BLEND 80 % SAO2
3 BLEND 90 % SAO2
3 DATA 70 % PULSE
3 DATA 80 % PULSE
3 DATA 90 % PULSE
3 DATA 70 % RSO2
3 DATA 80 % RSO2
3 DATA 90 % RSO2
3 DATA 70 % SAO2
3 DATA 80 % SAO2
3 DATA 90 % SAO2
Slope
Time Bins

Subject 3



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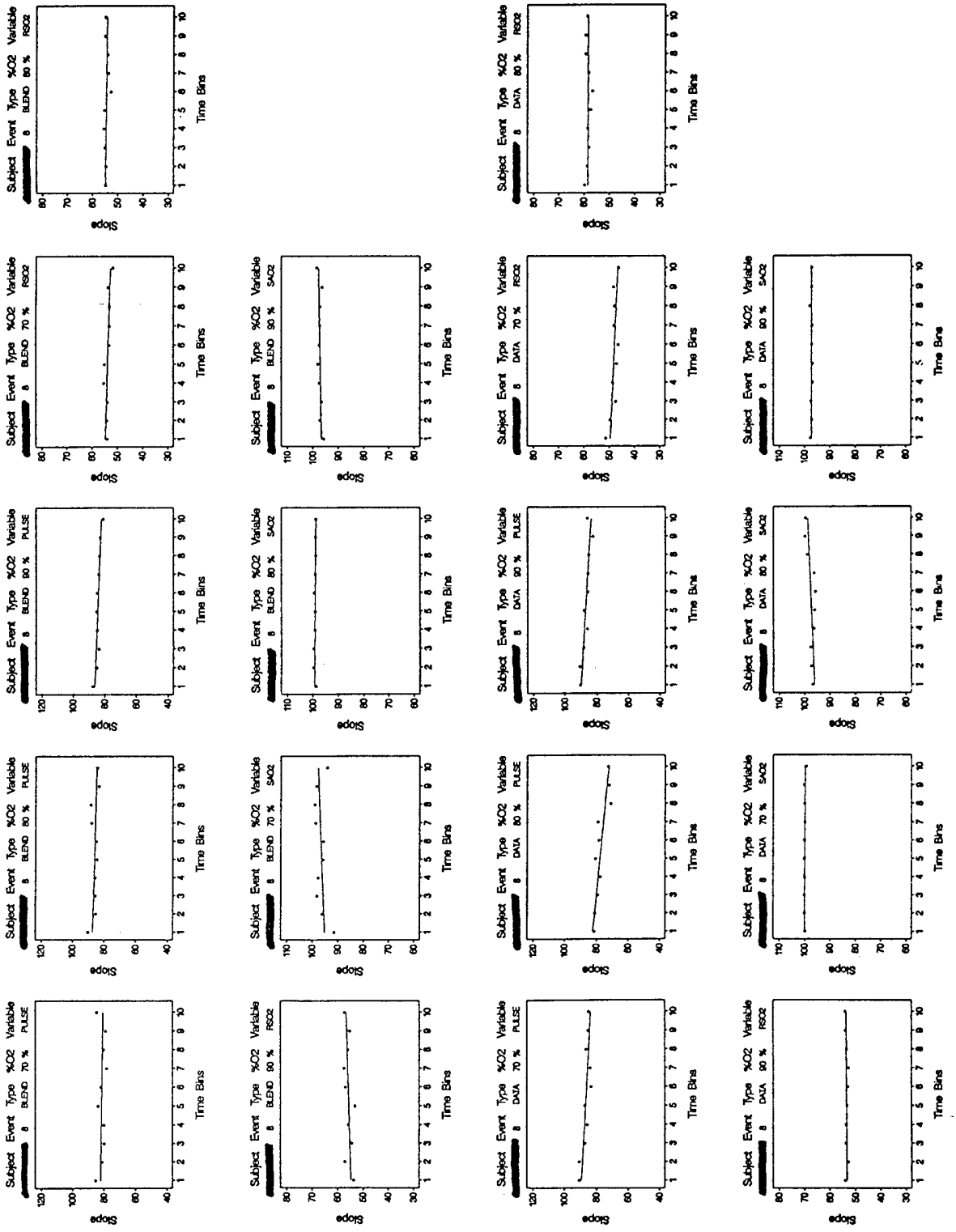

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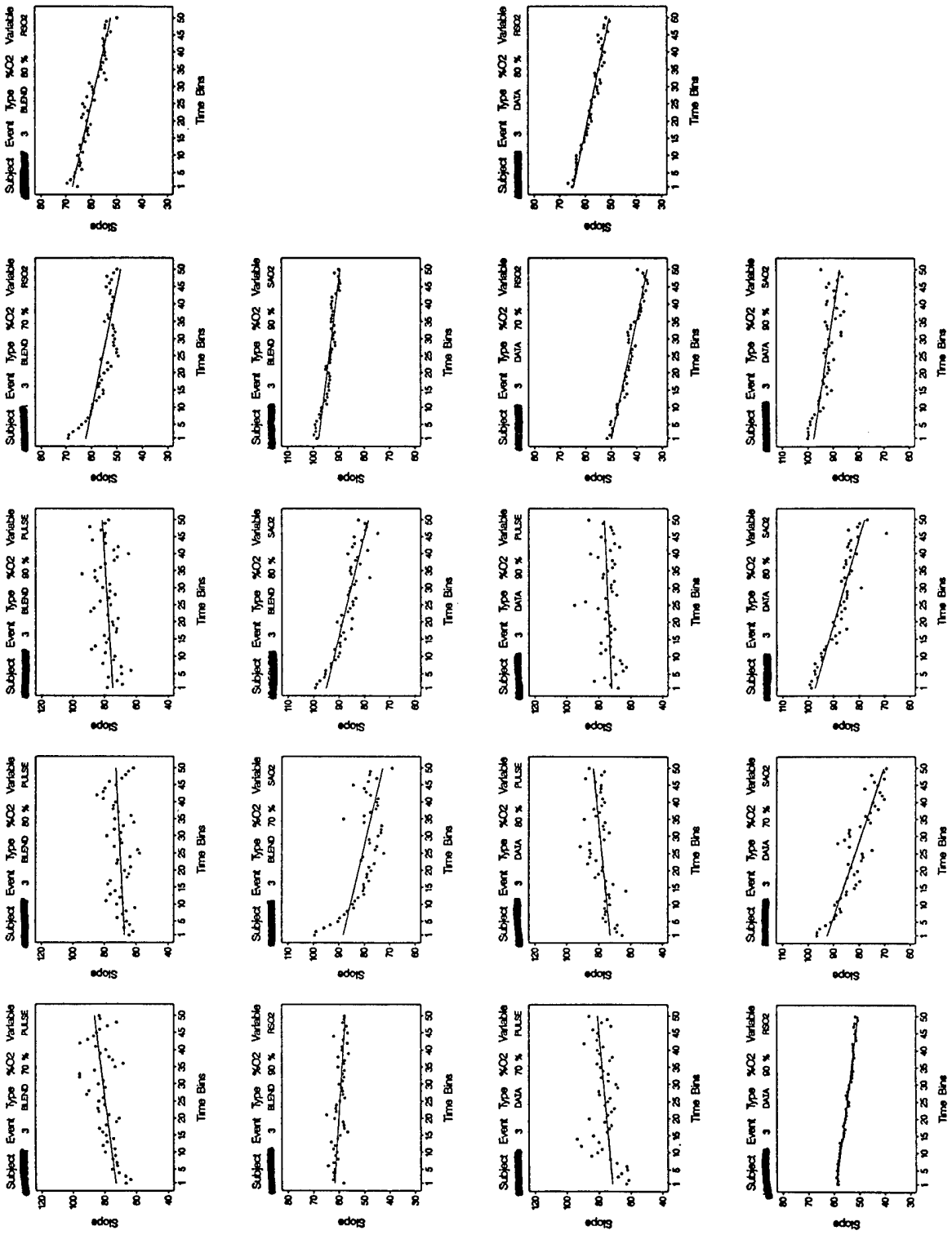

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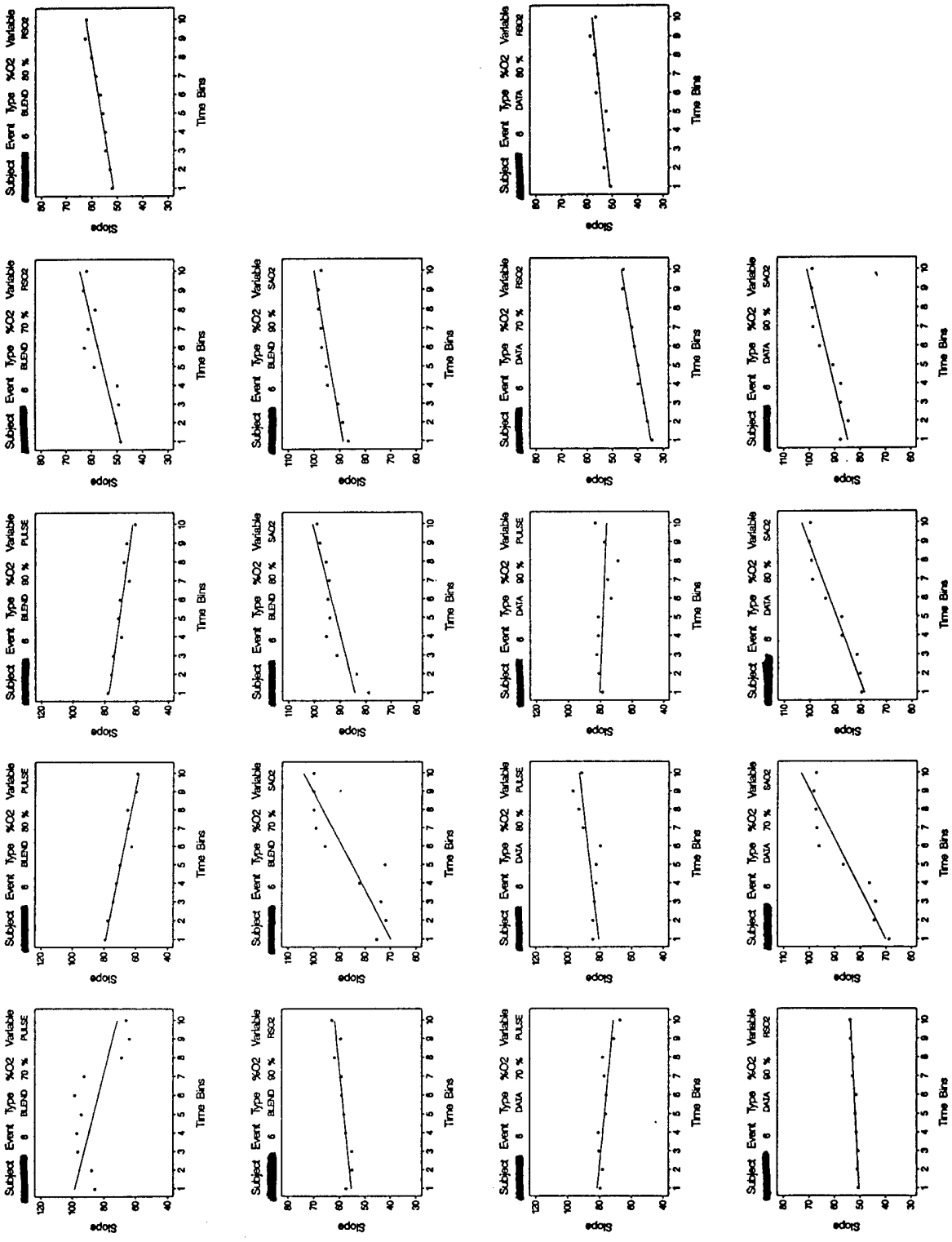

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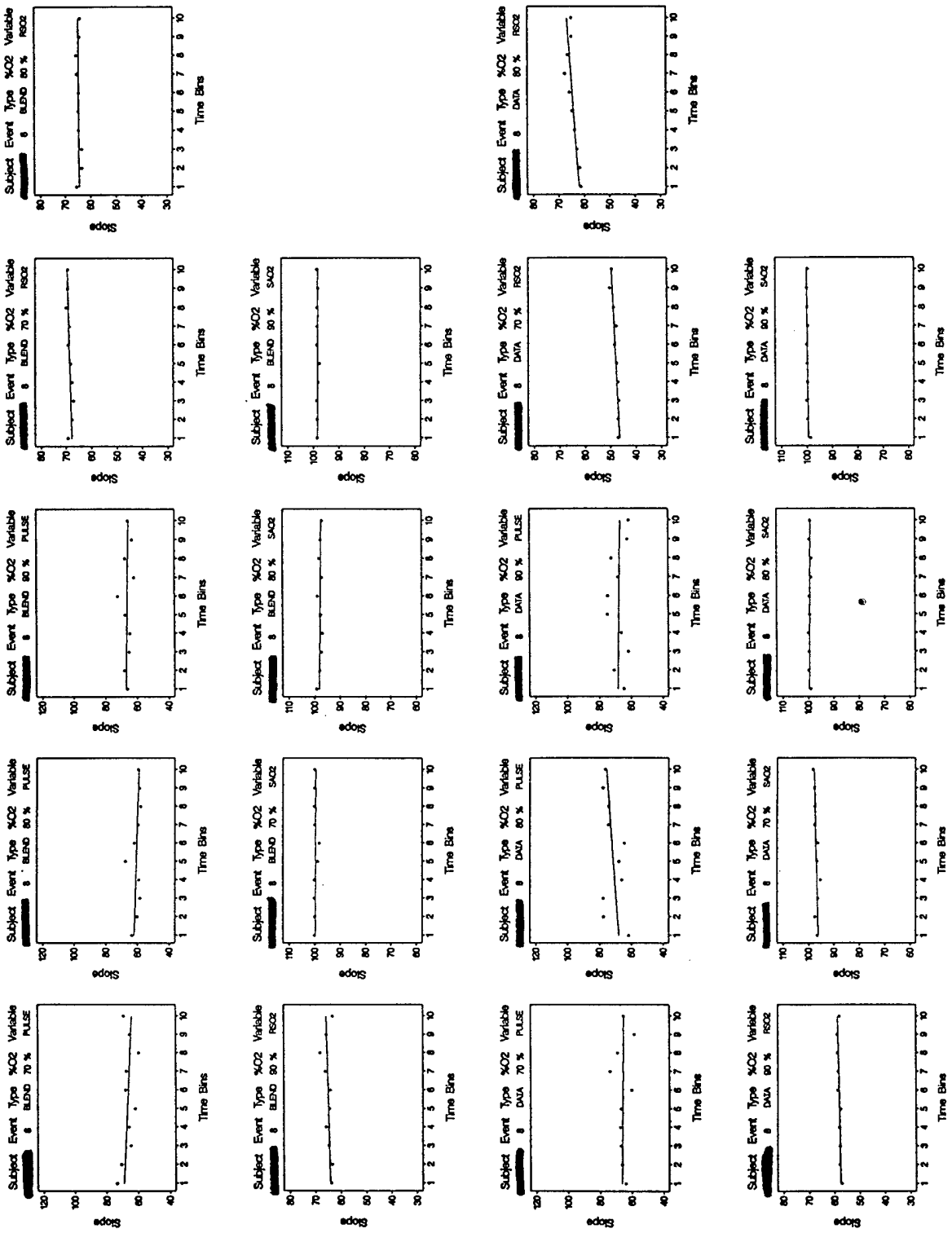

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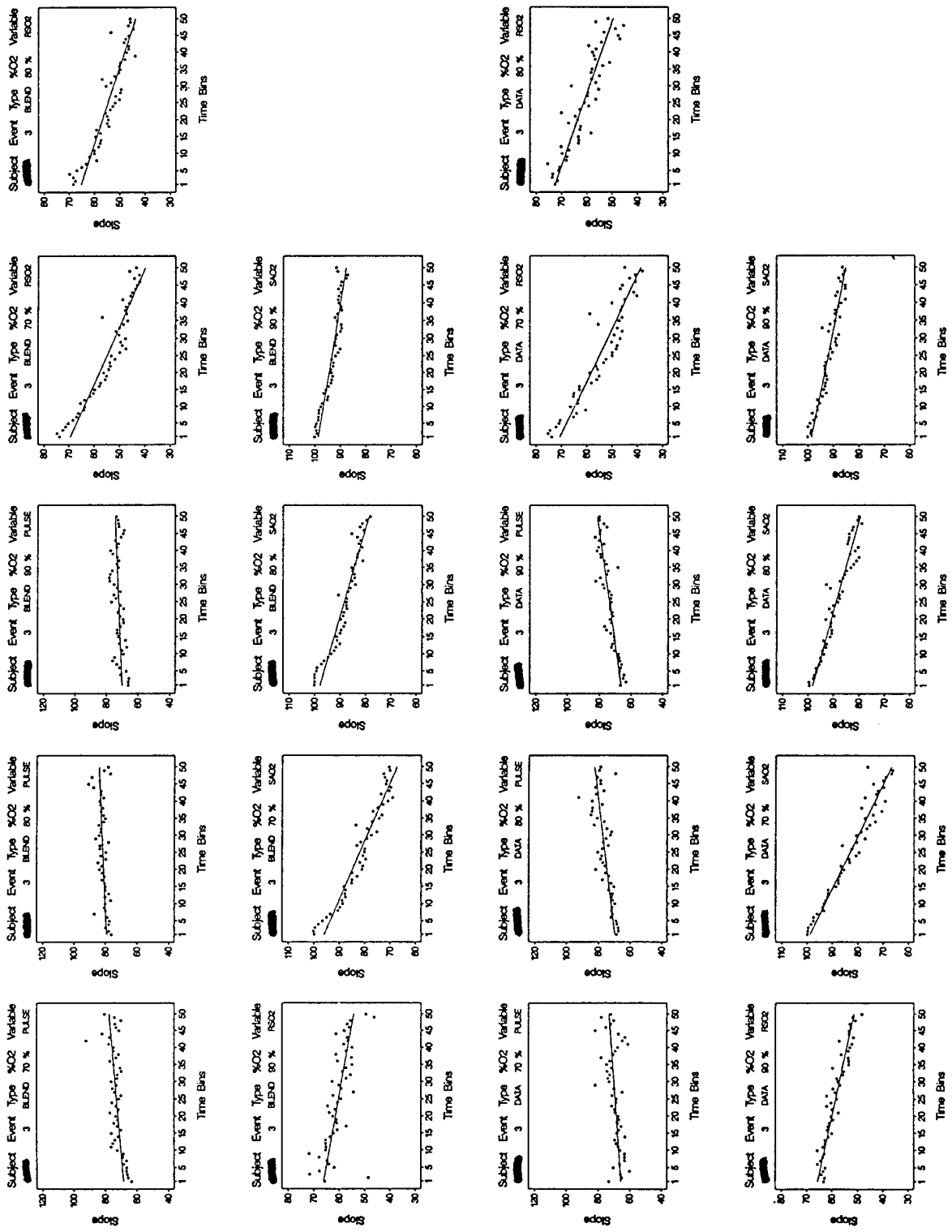

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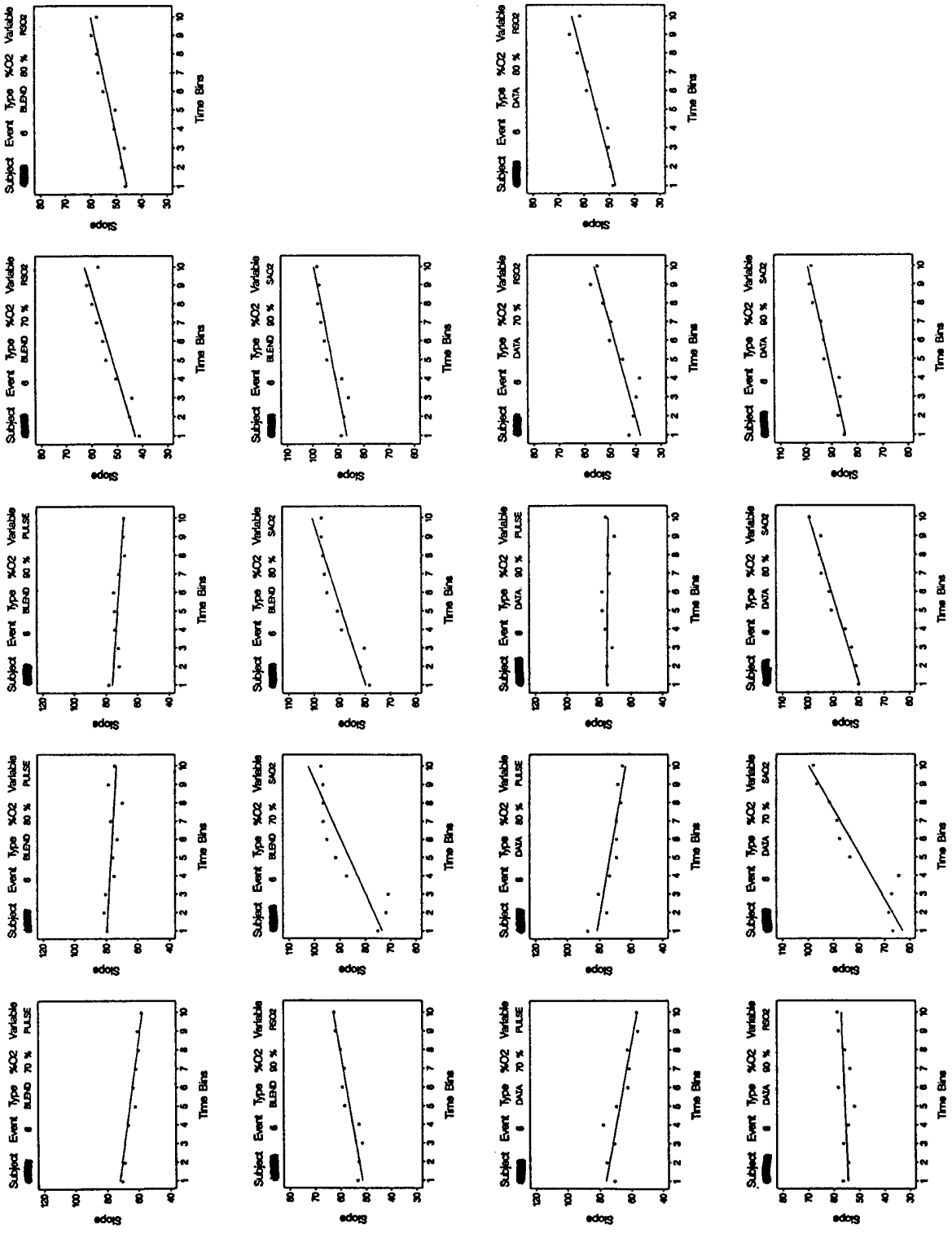
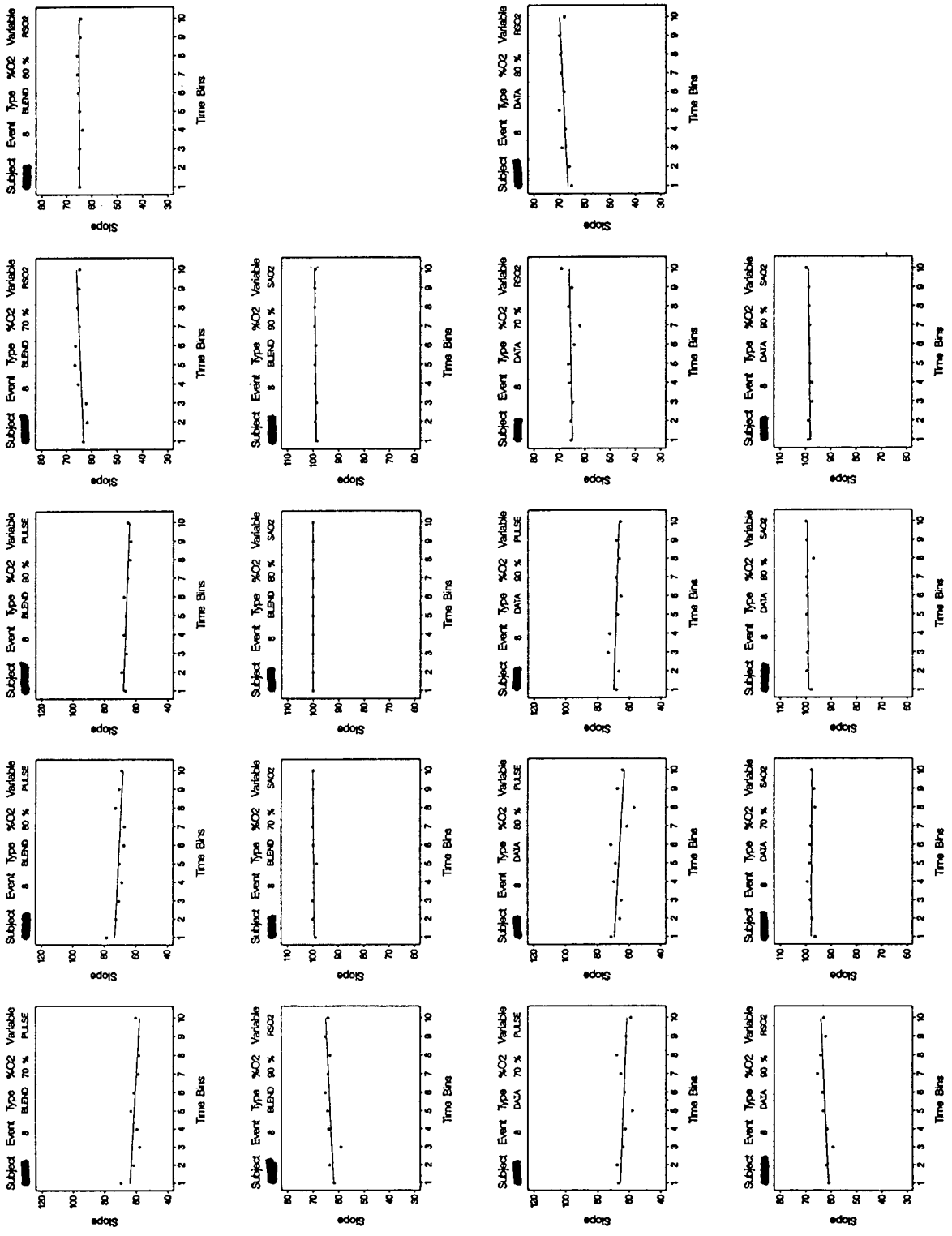


Subject 5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8 BLEND 70 % PULSE
8 BLEND 90 % PULSE
8 BLEND 80 % SAO2
8 BLEND 70 % SAO2
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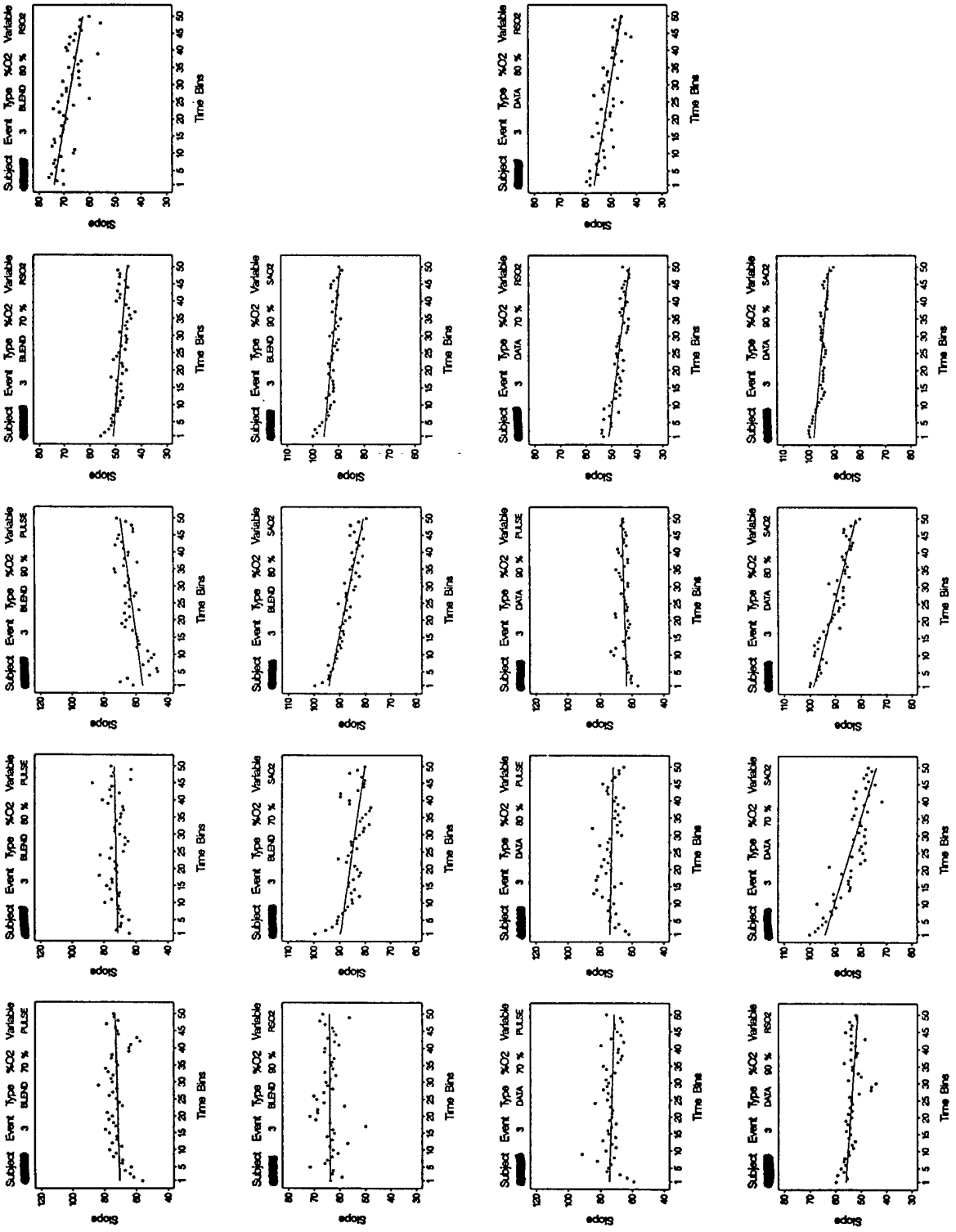
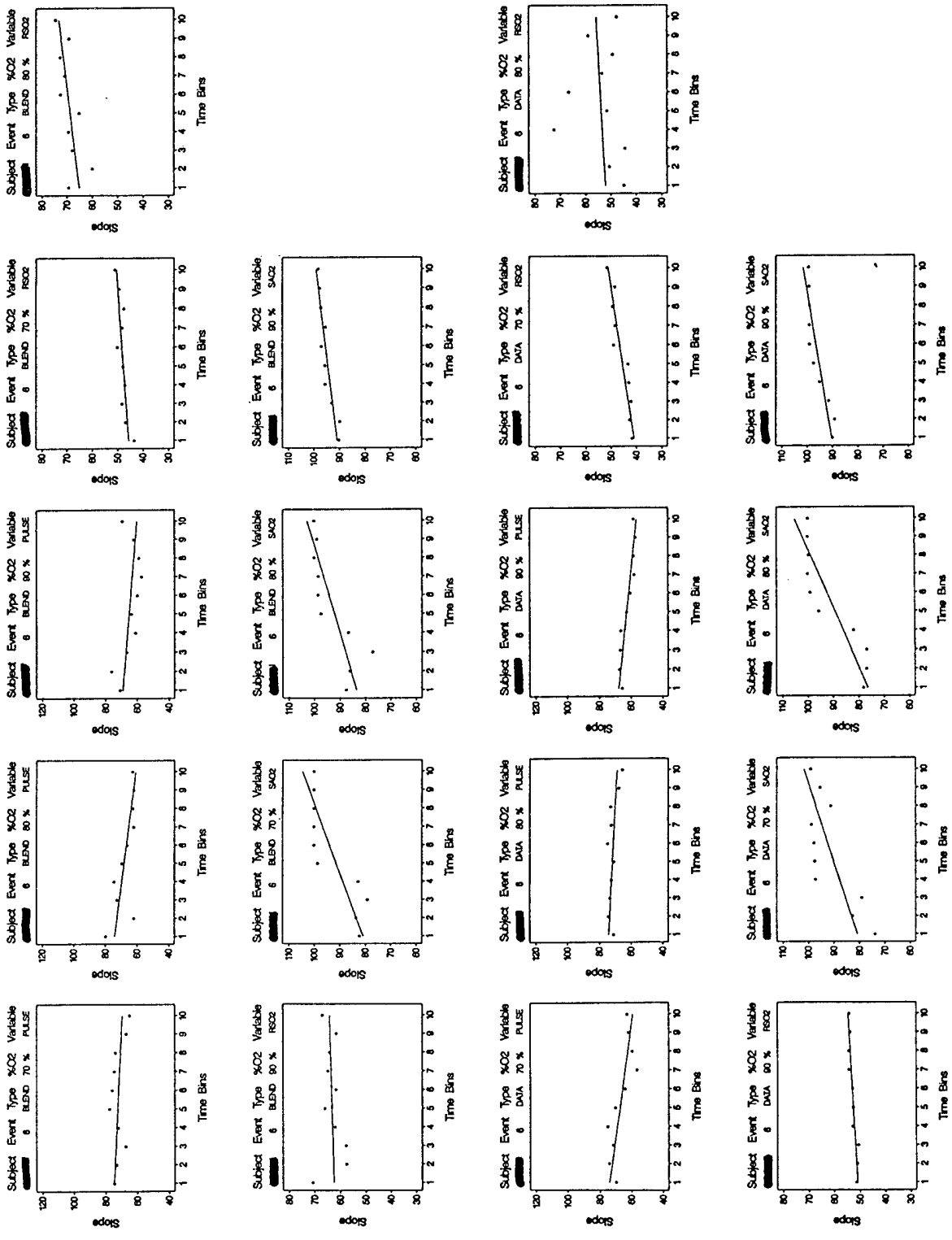
8 BLEND 80 % RSO2
8 BLEND 70 % RSO2
8 BLEND 90 % RSO2
8 DATA 80 % PULSE
8 DATA 70 % PULSE
8 DATA 90 % PULSE
8 DATA 80 % SAO2
8 DATA 70 % SAO2
8 DATA 90 % SAO2
8 DATA 80 % RSO2
8 DATA 70 % RSO2
8 DATA 90 % RSO2
Slope
Time Bins

# Subject 6



# Subject 6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6 BLEND 90 % PULSE
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6 BLEND 90 % RSO2
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6 BLEND 80 % SAO2
6 DATA 70 % PULSE
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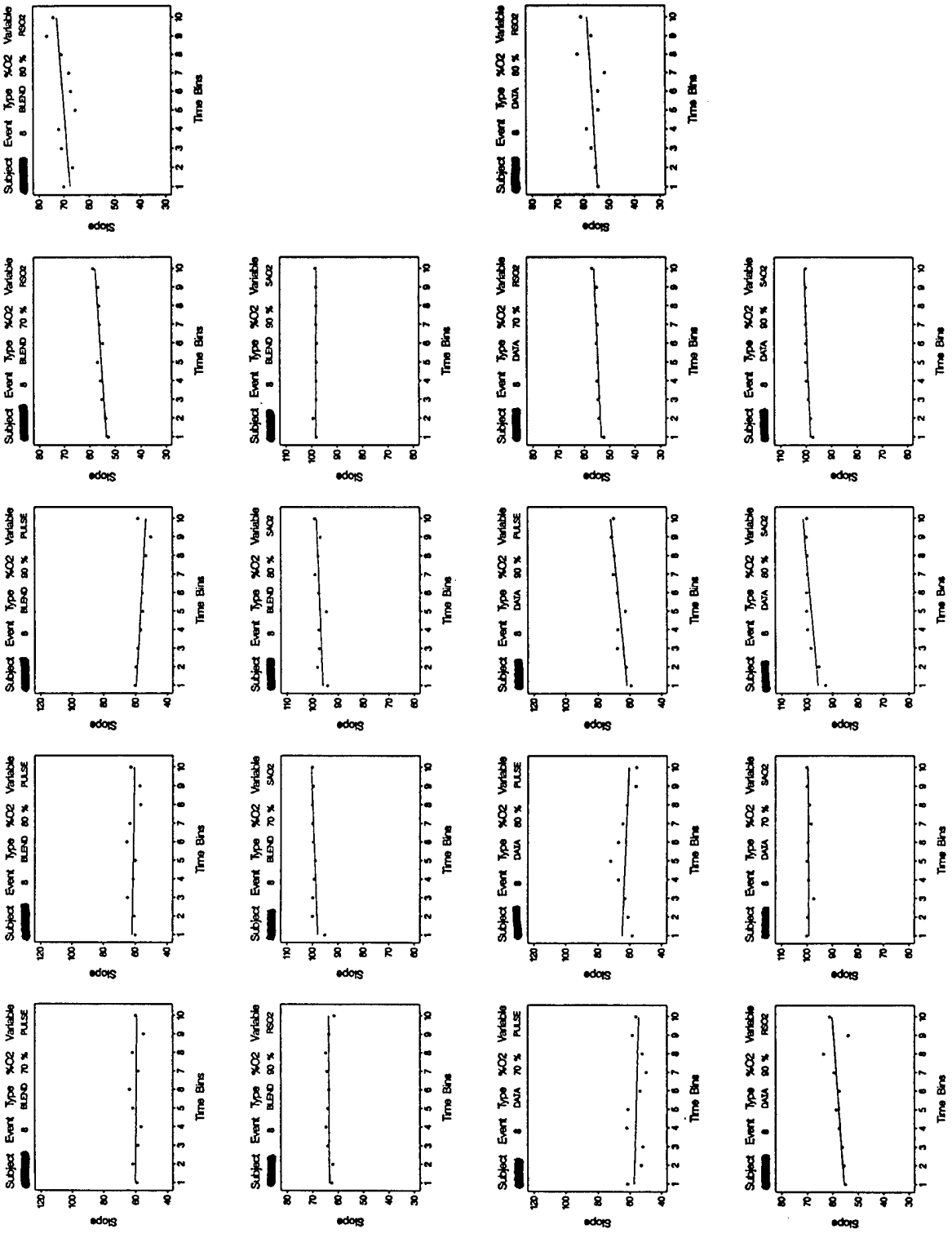
6 DATA 80 % RSO2
6 DATA 70 % SAO2
6 DATA 80 % SAO2
Slope
Time Bins

# Subject 6



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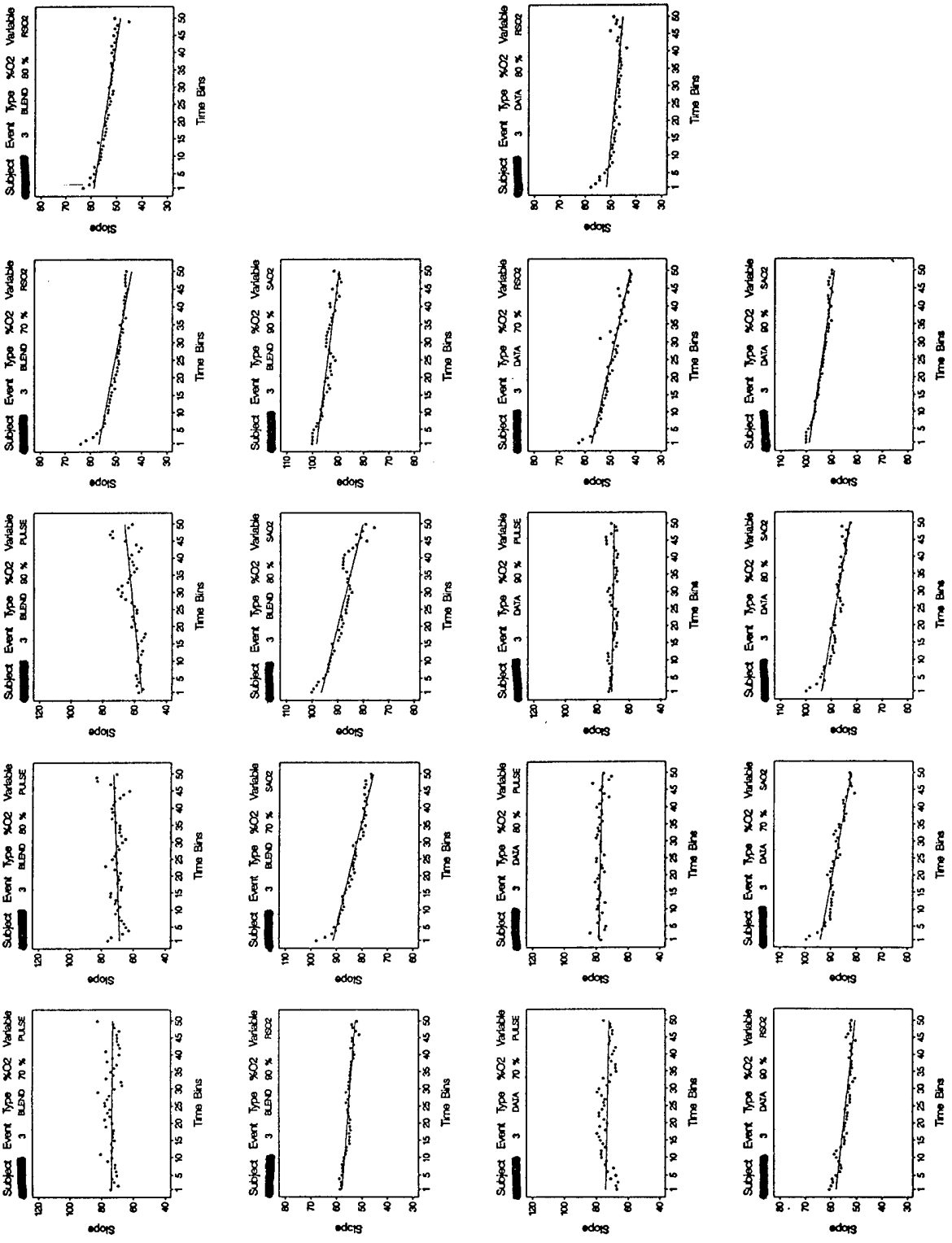
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3 BLEND 70 % RSO2
3 BLEND 90 % SAO2
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3 BLEND 80 % PULSE
3 BLEND 70 % PULSE
3 DATA 80 % RSO2
3 DATA 70 % RSO2
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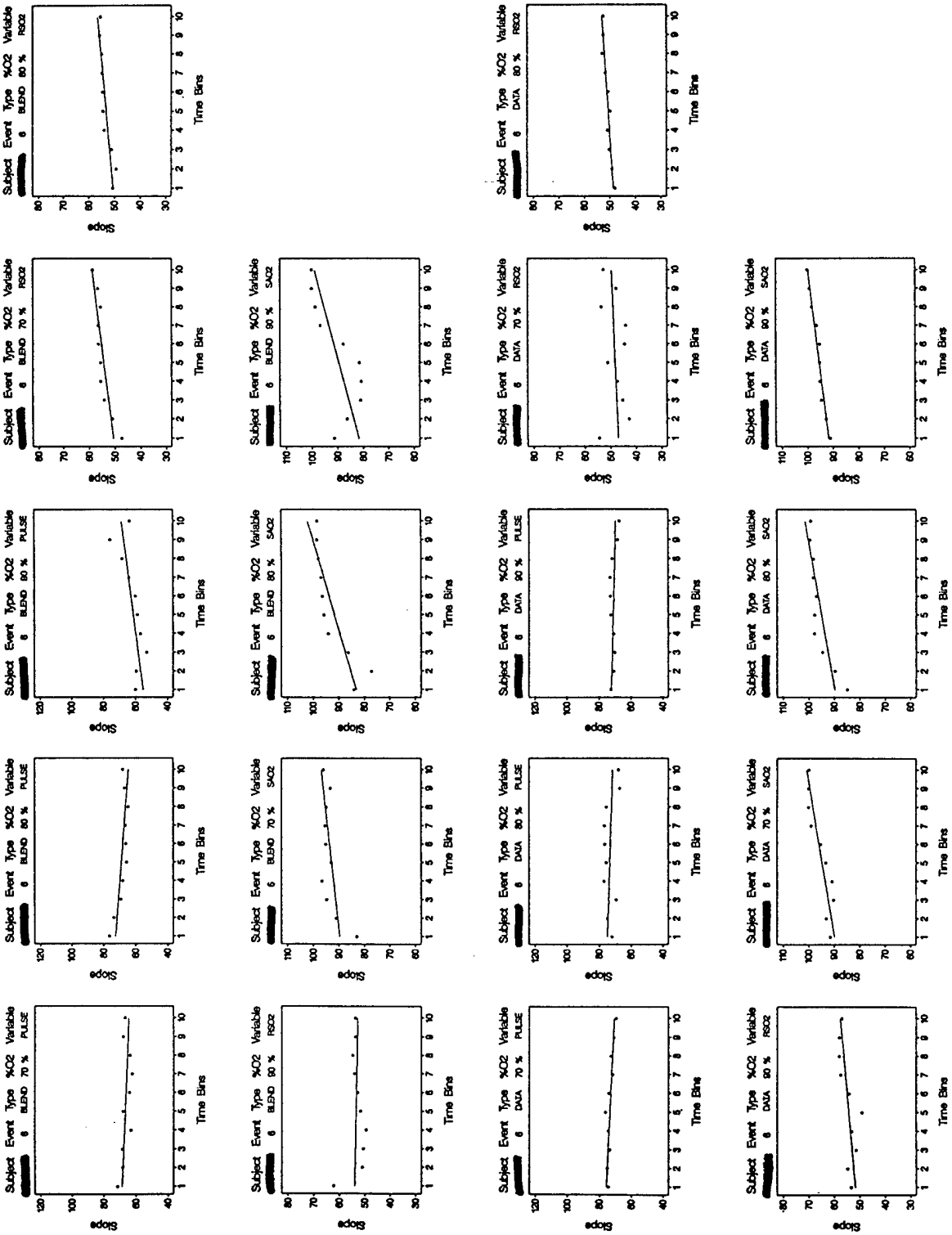
Slope
Time Bins

Subject 7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6 BLEND 80 % PULSE
6 BLEND 80 % SAO2
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6 DATA 80 % PULSE
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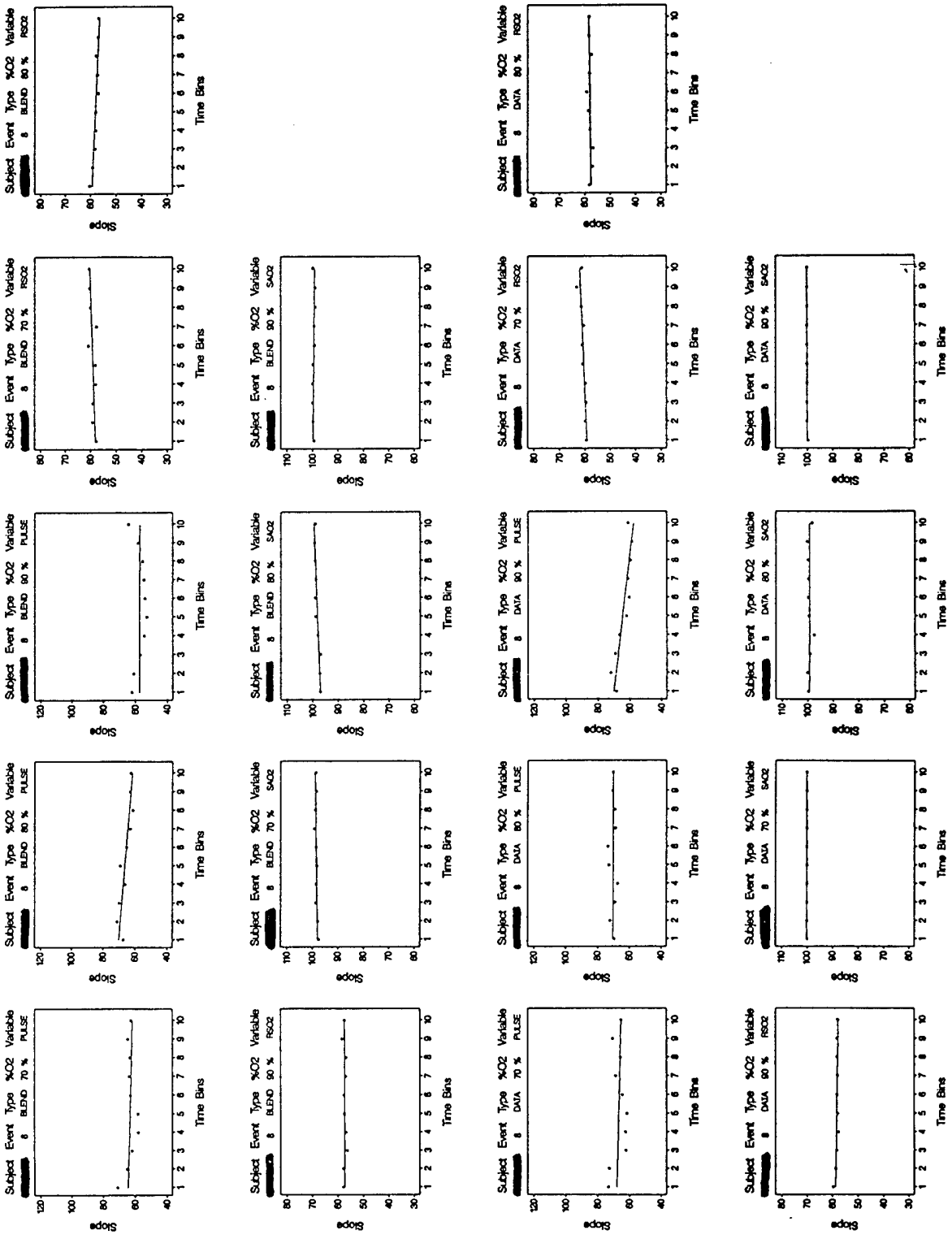
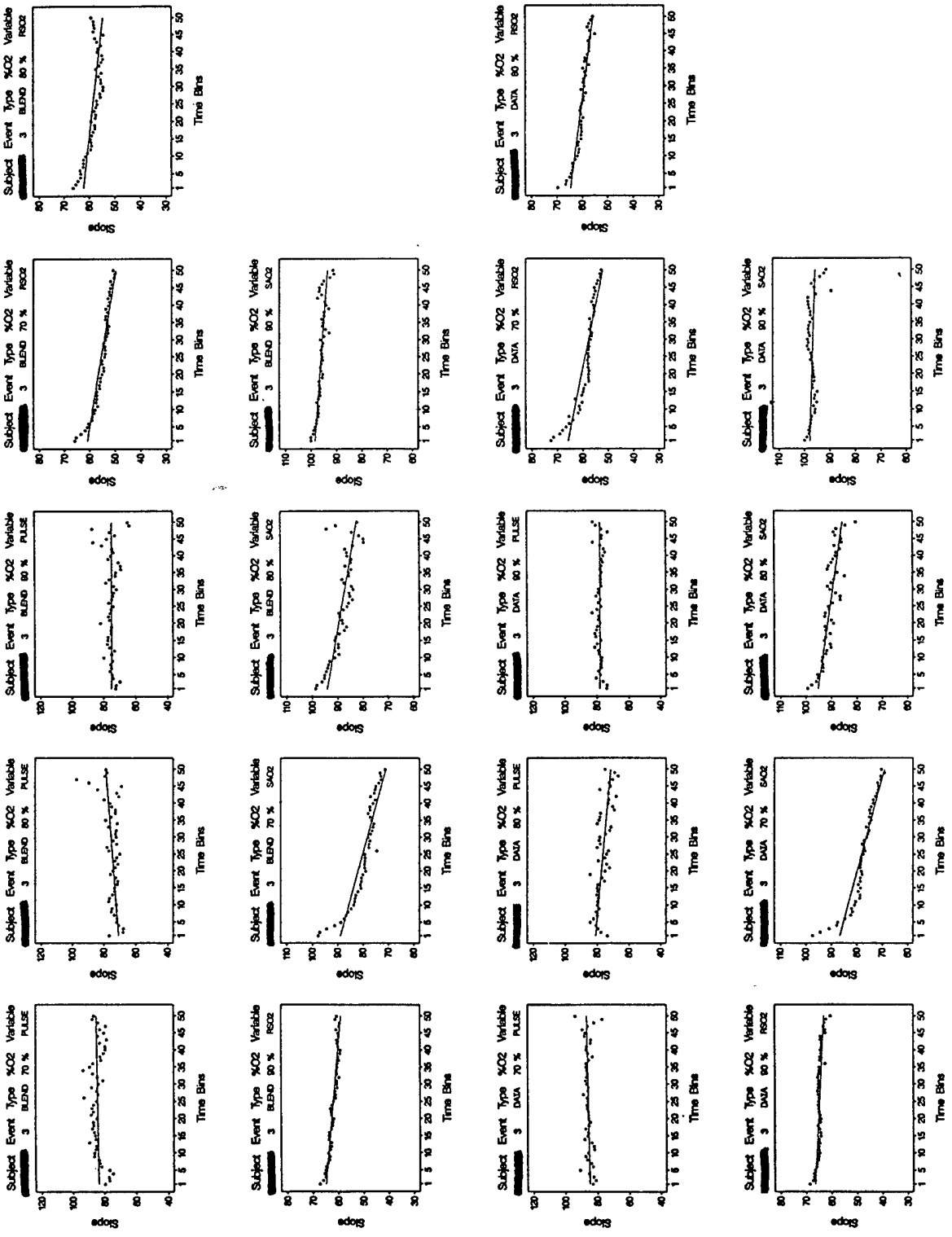
6 BLEND 70 % PULSE
6 BLEND 80 % RSO2
Slope
Time Bins

# Subject 7


Subject 8
Event
Type BLEND DATA
%O2 70 % 80 % 90 %
Variable RSO2 SAO2 PULSE
Slope
Time Bins

# Subject 8



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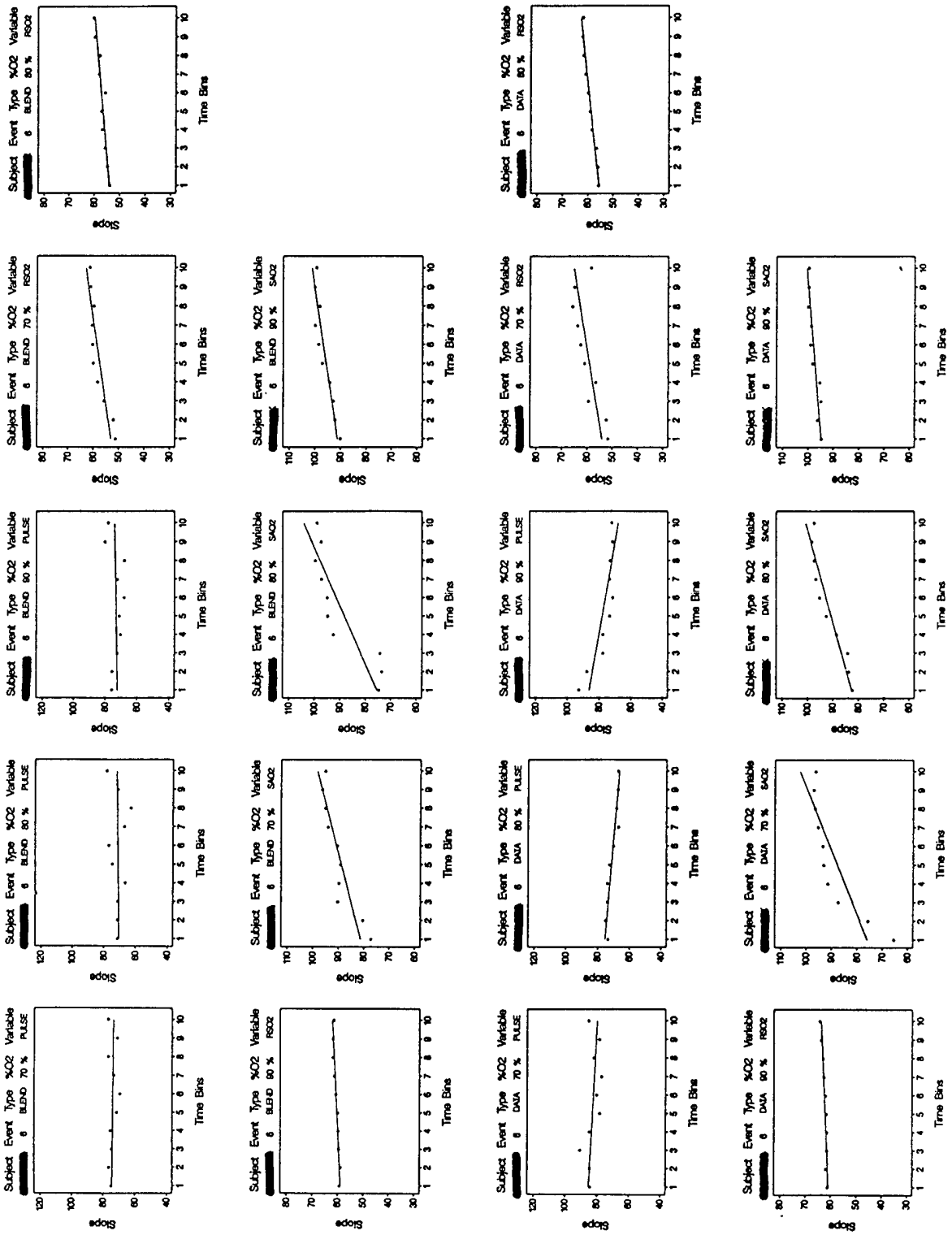

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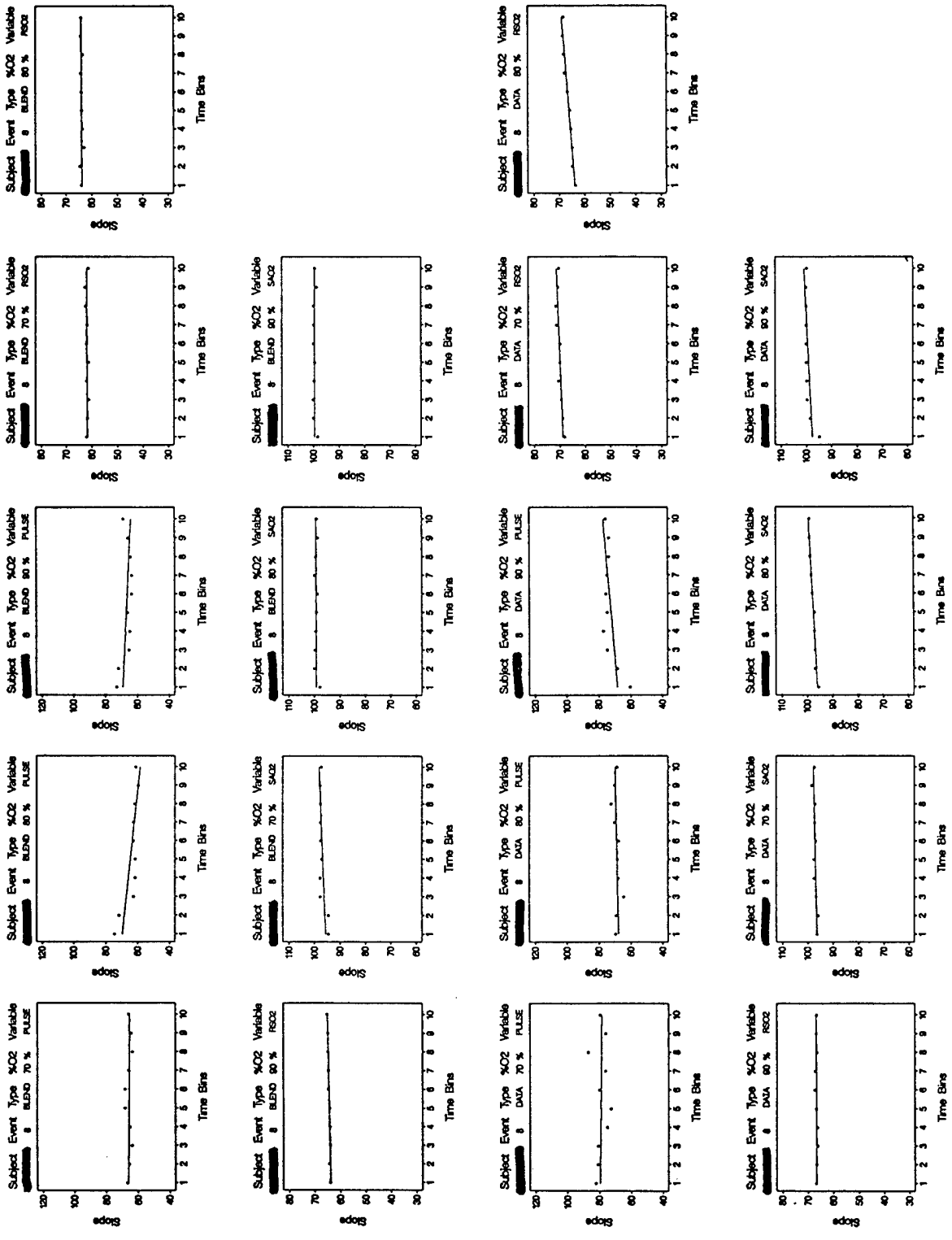

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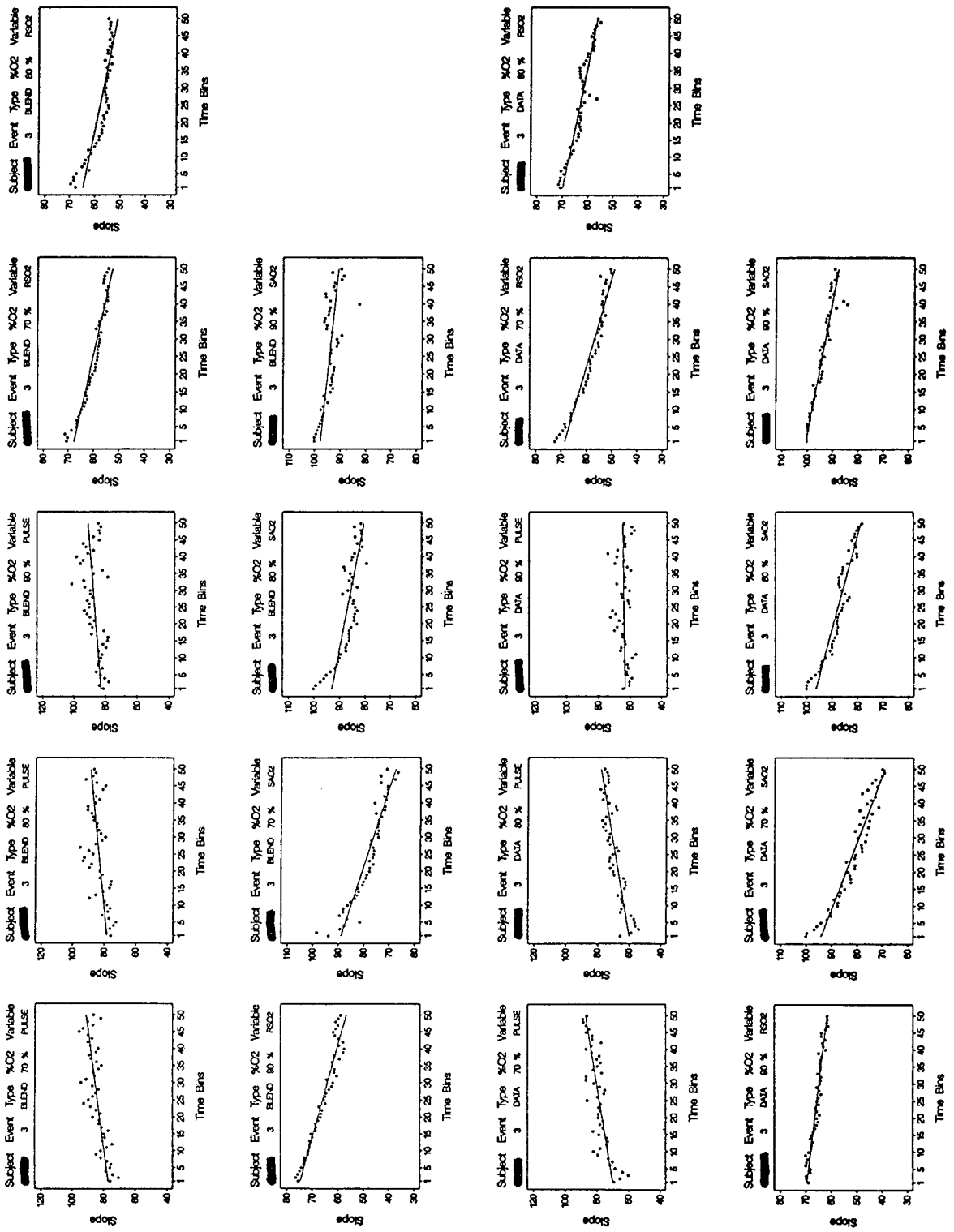
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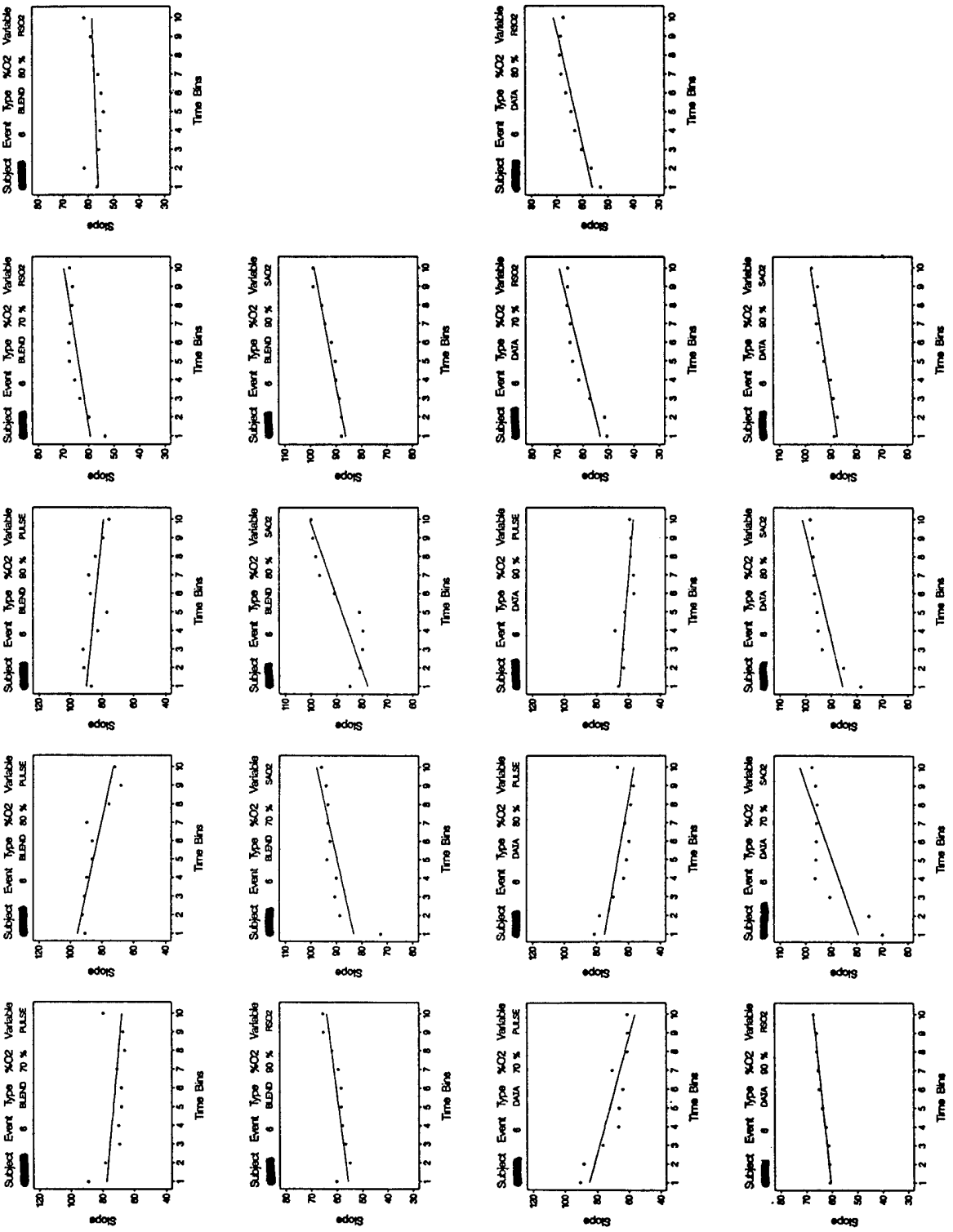
3 DATA 80 % RSO2
Slope
Time Bins

Subject 9



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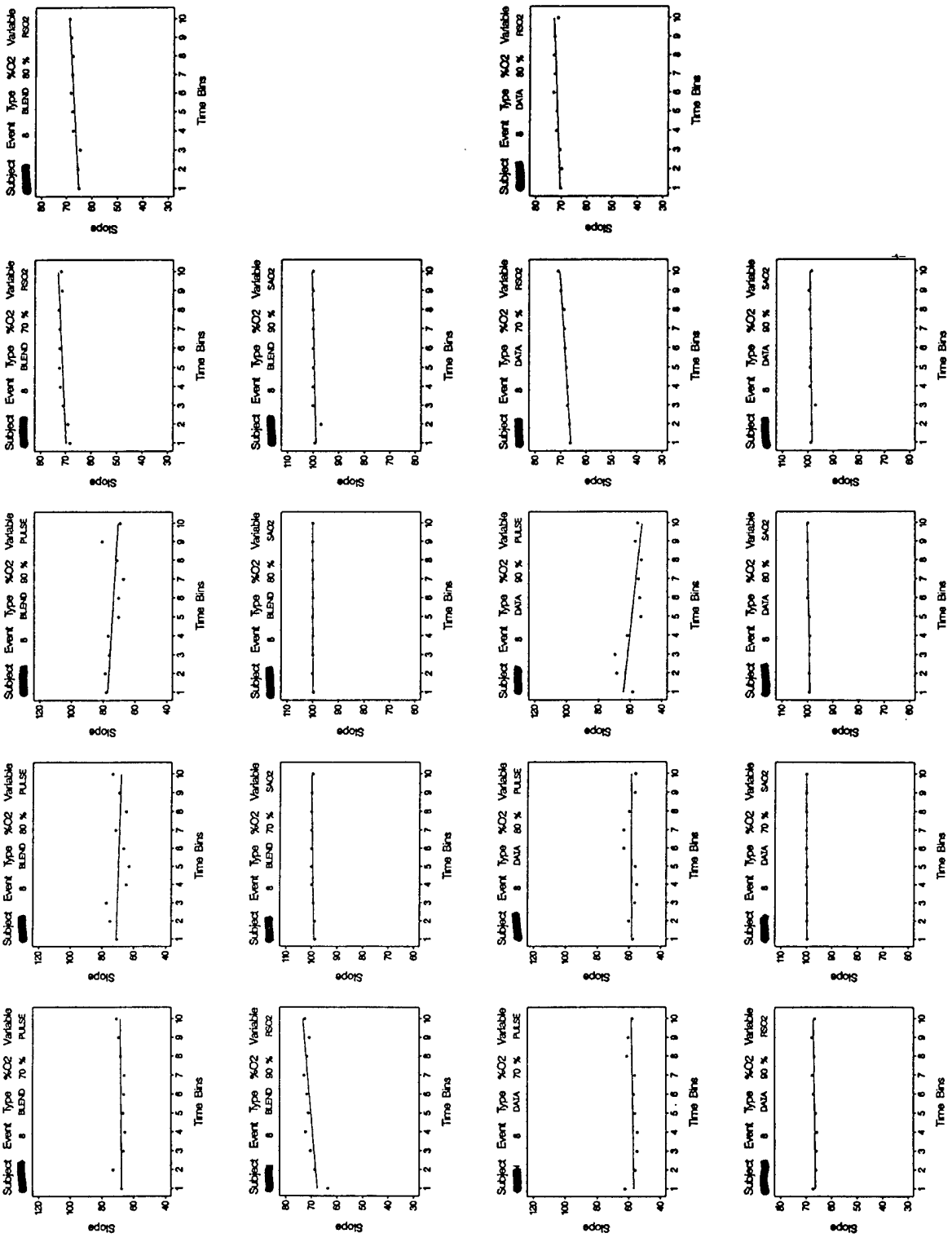

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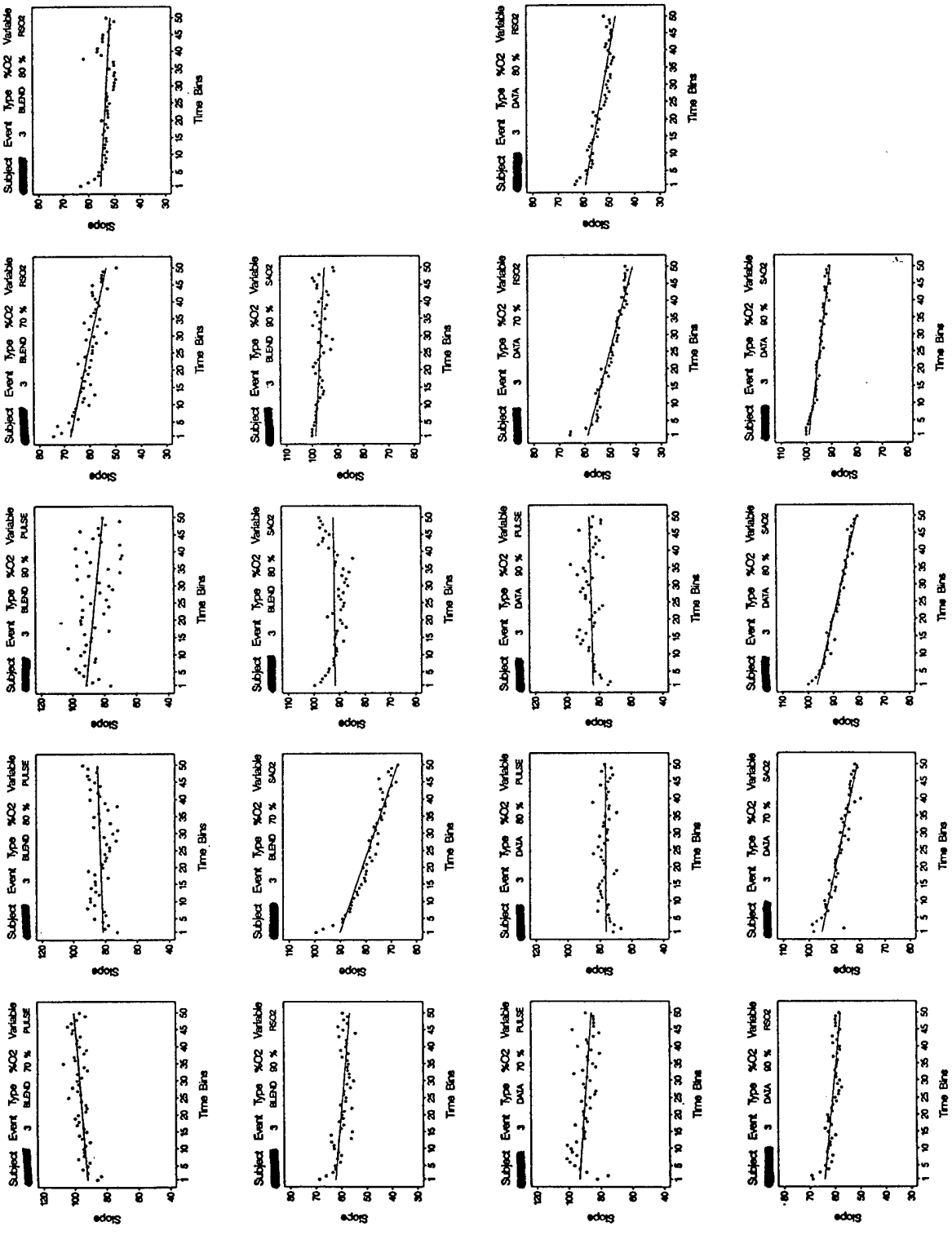
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3 BLEND 70 % RSO2
3 BLEND 80 % PULSE
3 BLEND 70 % PULSE
3 BLEND 80 % SAO2
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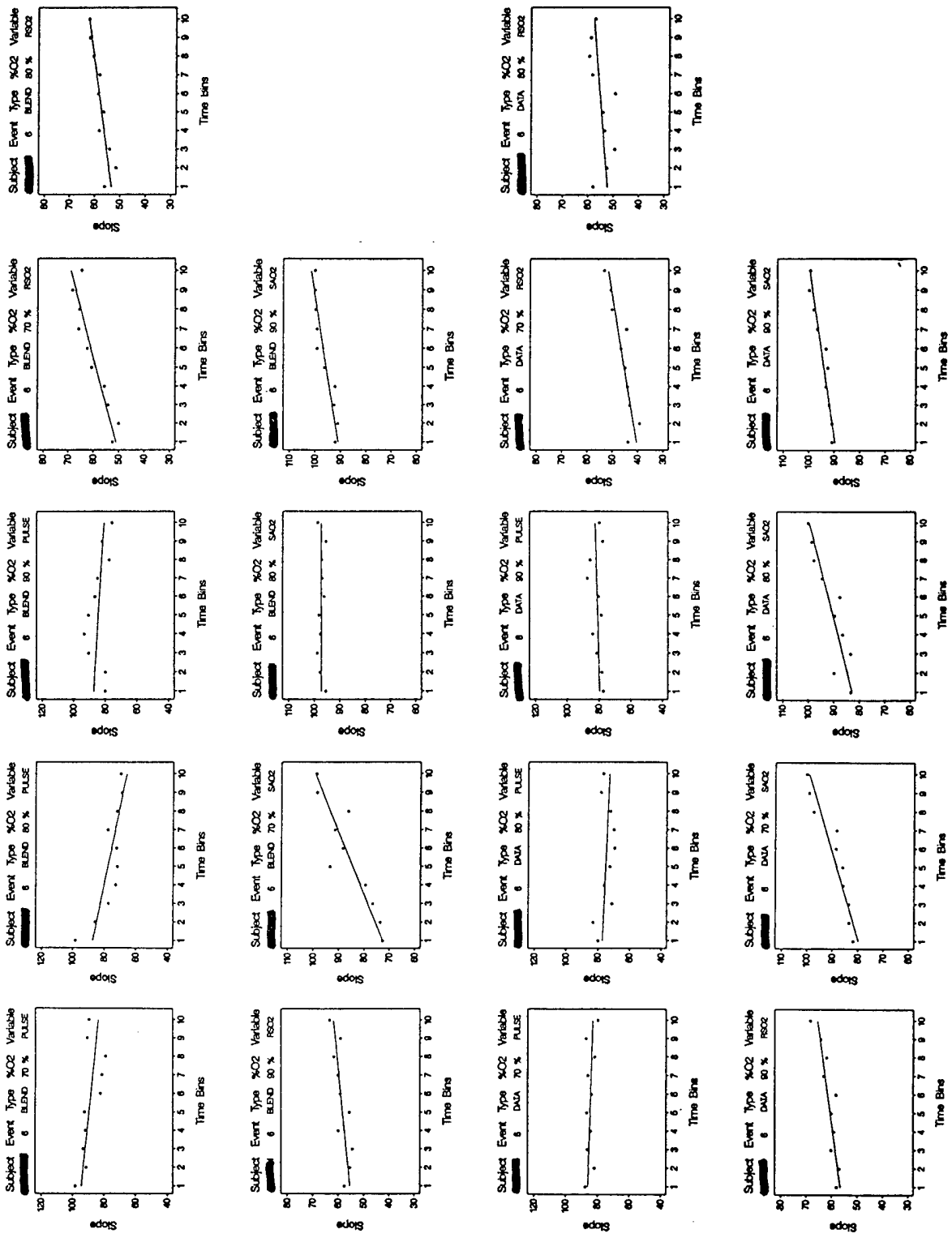
3 DATA 70 % RSO2
3 DATA 80 % PULSE
3 DATA 70 % PULSE
3 DATA 80 % SAO2
Slope
Time Bins

# Subject 10



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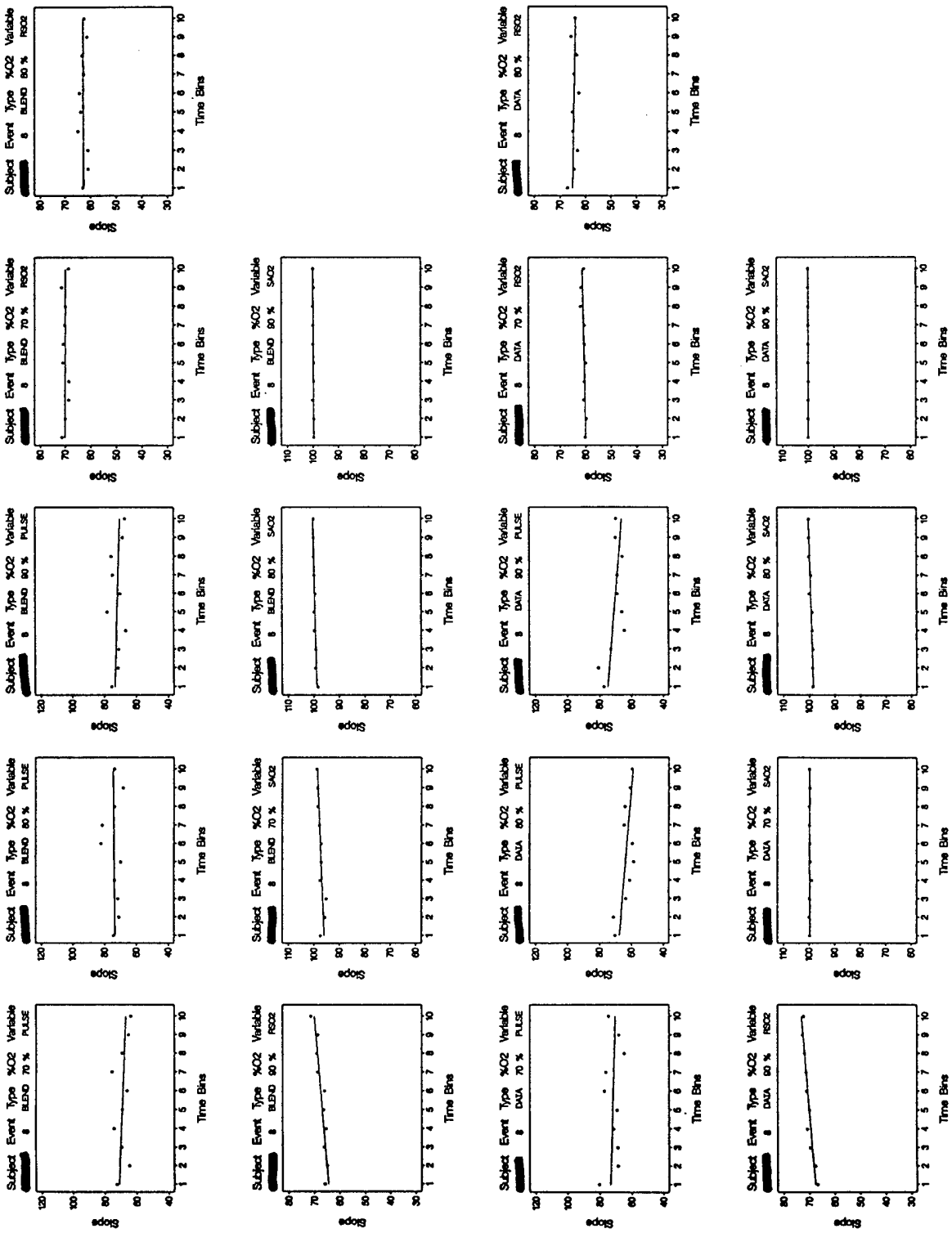

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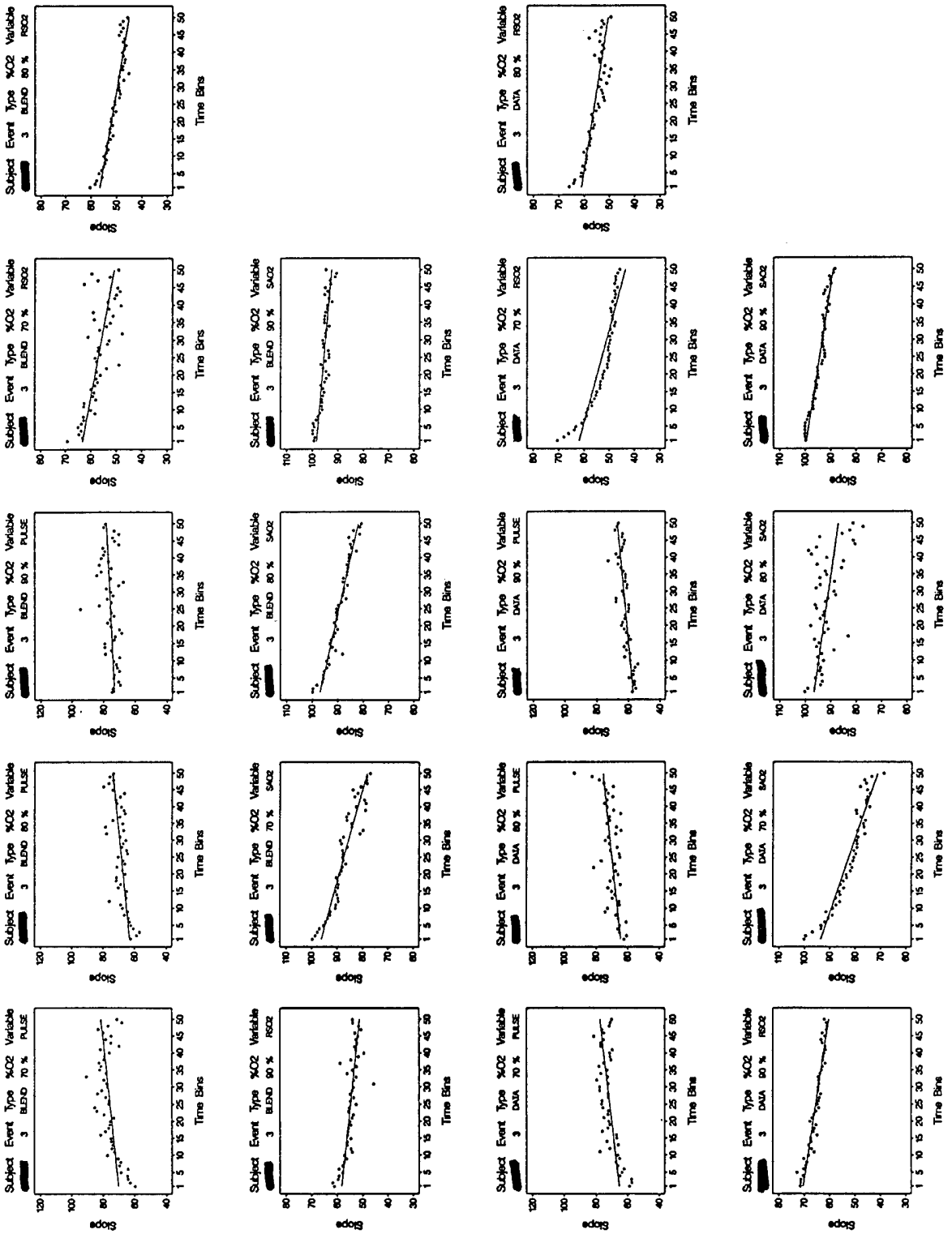

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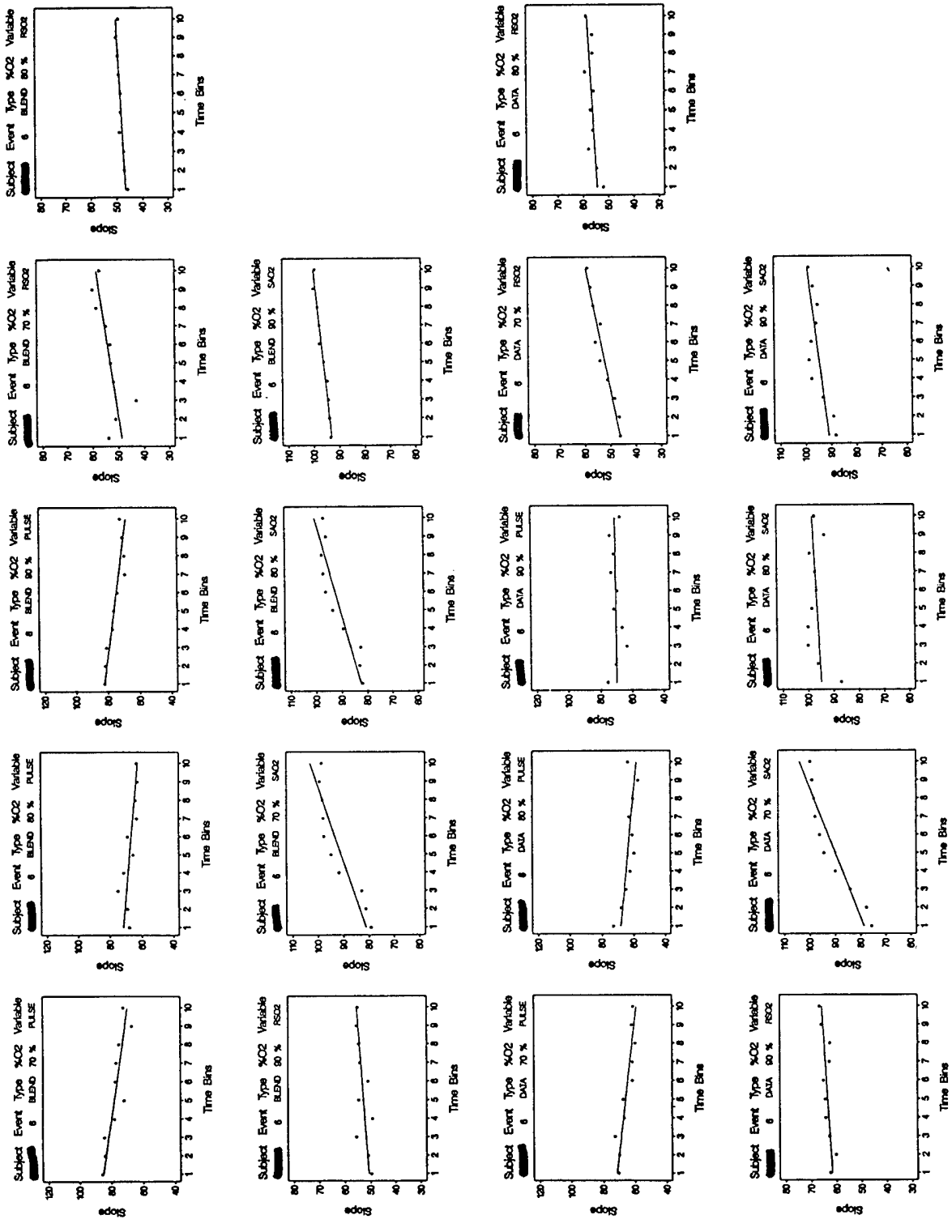

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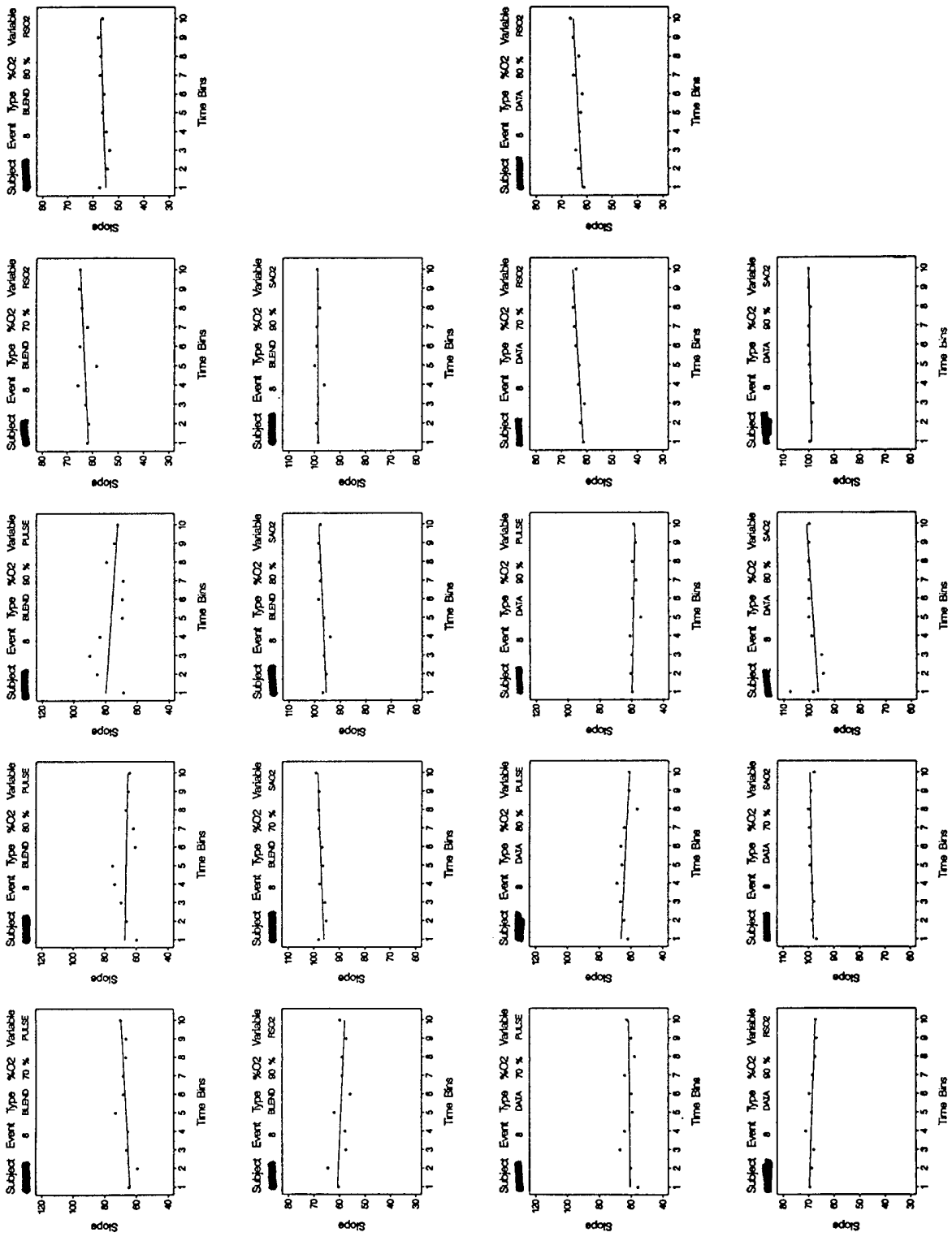

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